UNITED STATES
NUCLEAR REGULATORY COMMISSION
REGION I
475 ALLENDALE ROAD
KING OF PRUSSIA, PENNSYLVANIA 19406-1415

REAGENT KIT DISTRIBUTION APPROVAL

Du Pont Merck Pharmaceutical Company
Medical Products Department
331 Treble Cove Road
North Billerica, Massachusetts 01862

Approval No. 20-00320-17MA
Docket No. 030-10796
Amendment No. 18

In accordance with letter dated June 19, 1992, Approval No. 20-00320-17MA is amended in its entirely to read as follows:

1. The Reagent Kit(s) listed below are approved for distribution by Du Pont Merck Pharmaceutical Company to persons licensed pursuant to Section 35.14 and Section 35.100, Group III, of 10 CFR Part 35, (superseded) or Section 35.11 and Section 35.200 of 10 CFR Part 35 (effective April 1, 1987) or under equivalent licenses of Agreement States.

	Kit Trade Name	Radiopharmaceutical Prepared From Kit
A.	"Gluoscan TM" Technetium 99m Gluceptate Sodium Kit (NDA 17-907)	A. Technetium 99m labeled gluceptate sodium
B.	"Pulmolite TM" Technetium 99m Aggregated	B. Technetium 99m labeled aggregated albumin
C.	"Osteolite TM" Medronate Sodium Kit (NDA 17-972)	C. Technetium 99m labeled medronate sodium
D.	"Pyrolite TM" Stannous Pyrophosphate/ Trimetaphosphate Agent (NDA 17-684)	D. Technetium 99m labeled pyrophosphate/ trimetaphosphate sodium
E.	"Microlite TM" Technetium 99m Microaggregated Albumin Kit (NDA 18-263)	E. Technetium 99m labeled albumin colloid
F.	"Hepatolite TM" Technetium 99m Disofenin Kit (NDA 18-476)	F. Technetium 99m labeled Disofenin

G.	"Cardiolite TM" Technetium 99m RP30A (IND 28,333) (NDA 19-785)	G. Technetium 99m labeled 2-methoxyisobutyl isonitrile
H.	"Neurolite TM" Technetium Tc-99m RP-217A (IND 30,612)	H. Technetium 99m labeled N, N'-1,2-ethylenediylbis- L-cysteine diethyl ester (ECD)
I.	"DTPA" Technetium 99m DTPA Kit (NDA 17-264)	I. Technetium 99m labeled pentetate

2. The Reagent Kit(s) listed above shall be manufactured, packages, labeled, and distributed in accordance with statements, representations and procedures contained in letters dated January 28, 1988, April 21, 1988, December 7, 1990, March 13, 1991, January 15, 1992, and June 19, 1992, and October 6, 1992.

3. Any proposed changes in packaging, shielding, labeling, or the package insert shall be submitted to the U. S. Nuclear Regulatory Commission, Region I, Nuclear Materials Safety and Safeguards Branch, 475 Allendale Road, King of Prussia, Pennsylvania 19406.

4. Du Pont Merck Pharmaceutical Company, Medical Products Department is authorized to distribute Reagent Kits from 331 Treble Cover Road, North Billerica, Massachusetts.

5. Du Pont Merck Pharmaceutical Company, Medical Products Department shall notify the U. S. Nuclear Regulatory Commission within thirty (30) days of the termination of a "Notice of Claimed Investigation Exemption for a New Drug" (IND) or the withdrawal of approval of a "New Drug Application" (NDA) for any Reagent Kit(s) listed in Item 1 of this approval.

6. This approval shall expire on June 30, 1993.

For the U.S. Nuclear Regulatory Commission

Date OCT 29 1992

By Original Signed By:
Elizabeth Ullrich

Nuclear Materials Safety Branch
Region I
King of Prussia, Pennsylvania 19406

OCT 29 1992

License No. 20-00320-17MA
Docket No. 030-10796
Control No. 116768

Du Pont Merck Pharmaceutical Company
ATTN: Francis E. Roy, Jr.
331 Treble Cove Road
North Billerica, Massachusetts 01862

Dear Mr. Roy:

Please find enclosed an amendment to your NRC Material License.

Please review the enclosed document carefully and be sure that you understand all conditions. If there are any errors or questions, please notify the Region I Material Licensing Section, (215) 337-5093, so that we can provide appropriate corrections and answers.

Please be advised that you must conduct your program involving licensed radioactive materials in accordance with the conditions of your NRC license, representations made in your license application, and NRC regulations. In particular, please note the items in the enclosed, "Requirements for Materials Licensees."

Since serious consequences to employees and the public can result from failure to comply with NRC requirements, the NRC expects licensees to pay meticulous attention to detail and to achieve the high standard of compliance which the NRC expects of its licensees.

You will be periodically inspected by NRC. A fee may be charged for inspections in accordance with 10 CFR Part 170. Failure to conduct your program safely and in accordance with NRC regulations, license conditions, and representations made in your license application and supplemental correspondence with NRC will result in prompt and vigorous enforcement action against you. This could include issuance of a notice of violation, or in case of serious violations, an imposition of a civil penalty or an order suspending, modifying or revoking your license as specified in the General Policy and Procedures for NRC Enforcement Actions, 10 CFR Part 2, Appendix C.

OFFICIAL RECORD COPY - G:\WPS\MLTR\L2000320.17M - 10/19/92

ML 10

We wish you success in operating a safe and effective licensed program.

Sincerely,

Original Signed By:
Elizabeth Ullrich

for John D. Kinneman, Chief
Research Development and
Decommissioning Section
Division of Radiation Safety
and Safeguards

Enclosures:
1. Amendment No. 18
2. Requirements for Materials Licensees
3. 10 CFR Parts 2, 19, 20, 21, 30 and 170

DRSS:RI
Dimitriadis:mlb
10/21/92

DRSS:RI
Kinneman
10/21/92

The Du Pont Merck Pharmaceutical Company
Radiopharmaceutical Division
331 Treble Cove Road
N. Billerica, MA 01862
(508) 667 9531

M516
K-8

October 6, 1992

DU PONT
MERCK

United States Nuclear Regulatory Commission
Region I
Attn: Anthony Dimitriadis
Division of Radiation Safety and Safeguards
475 Allendale Road
King of Prussia, PA 19406

Reference: 1. Mail Control Number 116768
2. Materials License No. 20-00320-17MA

Dear Mr. Dimitriadis:

This is written in response to your verbal request for additional information concerning our license amendment for the above-referenced distribution approval.

I have attached for your review two sets of samples of the Neurolite™ package insert, the kit box label, the Vial A label and the Vial B label. These samples are originals generated by the printing company.

As stated in the letter dated June 19, 1992 the "Caution, Radioactive Material" label that is applied to the neck of the vial of the final preparation has not changed since the original submission of this label to your records on January 28, 1988.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy Jr.

Francis E. Roy, Jr.
Development Health Physicist

Telephone: (508) 671-8242

Toll Free: 1-800-362-2668, ext. 8242.

OFFICIAL RECORD COPY ML 10 116768

OCT 07 1992

DUPONT

March 1992

SAMPLE

The DuPont Merck Pharmaceutical Company
[illegible]
Billerica, Massachusetts 01862

NEUROLITE®
Kit for the Preparation of Technetium Tc99m Bicisate
for Diagnostic Use

DESCRIPTION: This kit formulation consists of two vials: Vial A contains Bicisate dihydrochloride (*N, N'*-1, 2-ethylenediylbis-L-cysteine diethyl ester dihydrochloride) and a reducing agent as a lyophilized solid, and Vial B contains a buffer solution. Each vial is sterile, non-pyrogenic and contains:

Vial A -

Bicisate dihydrochloride (ECD•2HCl)	0.90mg
Stannous chloride, dihydrate	0.072mg
Disodium EDTA, dihydrate	0.36mg
Mannitol	21 mg

Vial A is lyophilized and stored under nitrogen. The pH of the solution before lyophilization is 2.45 - 2.95. This vial is stored at room temperature (15-30°C).

Vial B -

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

Vial B is stored under air. The pH of the vial is 7.2 - 8.0. This vial is stored at room temperature (15-30°C).

This drug is administered by intravenous injection for diagnostic use after reconstitution with Sodium Pertechnetate Tc99m Injection. The precise structure of the Technetium complex is [*N, N'*-ethylendi-L-cysteinato(3-)]oxo[Tc99m] technetium (V), diethyl ester.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. Photons that are useful for the detection and imaging studies are listed in Table 1.

Table 1. Principle Radiation Emission Data

Radiation	Mean % / Disintegration	Mean Energy (KeV)
Gamma-2	89.07	140.5

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

Package Insert

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 Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of lead (Pb) is shown in Table 2. To facilitate control of the radiation exposure from MBq (mCi) amounts of this radionuclide, the use of a 0.25cm thickness of lead (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 time intervals after the time of calibration are shown in Table 3.

Table 3. Physical Decay Chart, Technetium Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fractions Remaining
0*	1.000	7	.447
1	.891	8	.398
2	.794	9	.355
3	.708	10	.316
4	.631	11	.282
5	.562	12	.251
6	.501		

*Calibration Time

CLINICAL PHARMACOLOGY: Technetium Tc99m Bicisate ([N, N'-ethylendi-L-cysteinato(3-)]oxo[Tc99m] technetium (V), diethyl ester) is well extracted by the monkey brain (4.7% I.D.) and is retained for a prolonged period post-injection ($T_{1/2}$ >24 hrs.) in the monkey brain. Autoradiographic studies of monkey brain show Technetium Tc99m Bicisate to be distributed according to regional cerebral blood flow in a pattern consistent with the standard tracer, ^{14}C iodoantipyrine.

The retention of Technetium Tc99m Bicisate in the CNS appears to be related to the relatively rapid metabolism of the parent compound in the brain. To date, the evidence for this is indirect. But, in monkey brain homogenates, the complex is metabolized completely to a single, less lipophilic component. The same metabolite was present in the cerebrospinal fluid of a monkey dosed intravenously with Tc99m Bicisate. Imaging and/or biodistribution studies in eight diverse species show prolonged retention of the agent only in the brains of the primate species. Finally, imaging of the metabolite of Tc99m Bicisate demonstrates the inability of this material to cross the blood-brain barrier, suggesting that if it is formed in the brain, the metabolite can not cross the blood-brain barrier in either direction.

The major organs in humans that retain Tc99m Bicisate or its metabolite are the brain, gallbladder, kidneys and liver. There is initial uptake in the lungs but this activity clears quickly. The initial brain uptake in humans is about 6% of the injected dose. Its half-life is about 27 hours.

The primary route of excretion of Tc99m Bicisate is the urinary tract. On average, 84% of the injected dose is cleared through the bladder during the first 24 hours post injection with up to 50% of the injected dose cleared within the first two hours. Approximately 11% of the injected dose is cleared through the G.I. tract over 48 hours.

INDICATIONS AND USAGE: Technetium Tc99m Bicisate may be useful for the determination of regional patterns of blood perfusion in the brain.

CONTRAINDICATIONS: None known.

WARNINGS: None known.

PRECAUTIONS: Patients should be encouraged to ingest fluids and to void frequently during the 2-6 hours immediately post injection in order to minimize radiation dose to the bladder.

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 preparative procedure.

GENERAL

Radioactive drugs must be handled with care and appropriate safety measures should be used 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 Tc99m 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc99m Bicisate affects fertility in males or females. Neurolite and its active ingredient bicisate dihydrochloride were tested in a battery of seven mutagenicity assays. Neurolite caused increases in unscheduled DNA synthesis in rat hepatocytes and sister chromatid exchanges in CHO cells in vitro. Neurolite did not cause gene mutations in the Salmonella/Ames and CHO/HPRT tests, nor did it cause chromosome aberrations in human lymphocytes in vitro. Bicisate dihydrochloride caused a borderline mutagenic response at the highest concentration of 5mg/plate in one out or four Salmonella test strains in the Ames assay. However, bicisate dinydrochloride did not show any mutagenic activity in the mouse micronucleus assay in vivo at doses up to 25mg/kg intravenously (>14000 times the maximum dose).

Pregnancy Category C

Animal reproduction and teratogenicity 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 reproductive capacity. There have been no studies in pregnant women.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature of a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

Technetium Tc99m 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 been established.

ADVERSE REACTIONS: In over 600 subjects, there were 4 cases of parosmia, all involving normal volunteers, at one site, who each reported a transient, mild, pleasant aromatic odor immediately after administration of Technetium Tc99m Bicisate. These were the only adverse events which were regarded as possibly related to the investigational drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Bicisate have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for intravenous administration, after preparation with fresh oxidant-free sodium pertechnetate Tc99m injection, in the average patient (70kg) is:

185-1665MBq (5-45mCi).

If the patient voids within 2 hours after the injection, a maximum of 1665MBq (45mCi) can be administered. A voiding interval of 4.8 hours allows for a maximum of 740MBq (20mCi) to be administered.

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 reconstitution, both Vial A and Vial B are to be stored at room temperature (15-30°C).

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

RADIATION DOSIMETRY: The radiation doses to organs and tissues of an average patient (70kg) per 1665MBq (45mCi) of Technetium Tc99m BICISATE injected intravenously are shown in Table 4.

Table 4. Radiation Absorbed Doses From Tc99m BICISATE

Organ	Estimated Absorbed Radiation Dose[2] mGy/1665 MBq (rads/45 mCi) 2.0 Hr. Void	mGy/740 MBq (rads/20 mCi) 4.8 Hr. Void
Brain	9.2 (0.9)	4.0 (0.4)
Gallbladder Wall	40.9 (4.1)	18.2 (1.8)
Lower Large Intestine Wall	21.2 (2.1)	11.1 (1.1)
Small Intestine	15.7 (1.6)	7.5 (0.8)
Upper Large Intestine Wall	27.4 (2.7)	12.4 (1.2)
Kidneys	12.1 (1.2)	5.3 (0.5)
Liver	8.8 (0.9	4.0 (0.4)
Lungs	3.4 (0.3)	1.3 (0.1)
Ovaries	9.9 (1.0)	5.7 (0.6)
Red Marrow	3.9 (0.4)	1.7 (0.2)
Bone Surfaces	5.8 (0.6)	2.6 (0.3)
Testes	3.6 (0.4)	2.6 (0.3)
Thyroid	5.8 (0.6)	2.6 (0.3)
Urinary Bladder Wall	49.5 (4.9)	53.7 (5.4)
Total Body	4.0 (0.4)	2.2 (0.2)

[2]Dosimetry calculated using the MIRD program at Oak Ridge Associated Universities.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m BICISATE

Preparation of the Technetium Tc99m Bicisate from the Kit for the Preparation of Technetium Tc99m Bicisate is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m injection to vial B, 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 (100mCi) sterile, non-pyrogenic Sodium Pertechnetate Tc99m injection, in approximately 2.0 mL, to vial B.

e. With a sterile syringe, rapidly inject 3.0 mL of Sodium Chloride Injection into vial A to dissolve the contents. Shake the contents of the vial for a few seconds.

f. With another sterile syringe, immediately (within 30 seconds) transfer 1.0 mL of vial A to vial B.

g. Swirl the contents of the vial for a few seconds, and allow this mixture to stand for thirty minutes at room temperature.

h. Examine the vial contents for particulates and discoloration prior to injection.

i. Aseptically withdraw the required dose using a sterile shielded syringe. Use within six hours of preparation.

j. Radiochemical purity should be checked prior to patient administration.

DETERMINATION OF RADIOCHEMICAL PURITY

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

MATERIALS FOR TLC PROCEDURE

Baker-Flex silica gel IBF, 2.5 x 7.5 cm, Baker #2-4463
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 of the final solution by the thin layer chromatography (TLC) using Baker-Flex silica gel IBF plates and a solvent system of ethyl acetate.

Procedure - Using fresh ethyl acetate pour enough solvent into the developing tank to a depth of 3 to 4 mm. Seal the tank with Paratilm 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.

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 guage 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.

The plate is then placed in the pre-equilibrated TLC tank and developed to the 7.0 cm line (about 15 minutes). The plate is removed and dried in a ventilated area.

Quantification

Cut the TLC plate 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 Tc99m Bicisate and the bottom portion contains all radioimpurities.

Calculate the radiochemical purity using the following equation:

$$\% \text{ Tc99m Bicisate} = \frac{\text{Activity on top portion}}{\text{Activity on Top + Bottom}} \times 100$$

Criteria

Tc99m Bicisate has an Rf of 0.9 +/- 0.1; Colloid, TcO_4^-, Tc99m EDTA- and Tc(IV) ECDremain at the origin. If the radiochemical purity is less than 90%, do not use the kit and discard the preparation.

HOW SUPPLIED: Du Pont's Kit for the Preparation of Technetium Tc99m Bicisate is supplied in kits of 10 vials, five (5) vialr of A and five (5) vials of B. Included in each kit is one (1) package insert and ten (10) radiation labels.

Both Vial A and Vial B are stored at room temperature (15-30°C).

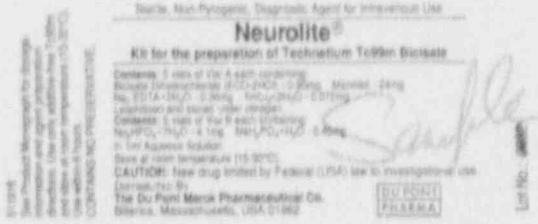
Store at room temperature (15-30°C) after preparation procedure.

This reagent kit is supplied under IND #30,612 or other appropriate clinical research license. This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.200, 10 CFR Part 35 or under equivalent licenses of Agreement States.

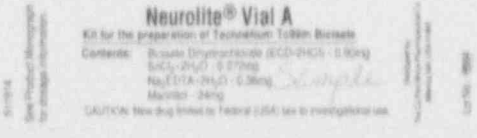
Supplied By

The DuPont Merck Pharmaceutical Company
331 Treble Cove Road
Billerica, Massachusetts 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 508-667-9531)

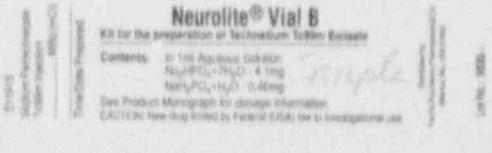
513059



KIT BOX LABEL



VIAL A LABEL



VIAL B LABEL

CONVERSATION RECORD

TIME 2:04 PM | DATE 09/21/92

TYPE: ☐ VISIT ☐ CONFERENCE ☒ TELEPHONE ☐ INCOMING ☒ OUTGOING

Location of Visit/Conference:

NAME OF PERSON(S) CONTACTED OR IN CONTACT WITH YOU	ORGANIZATION (Office, dept., bureau, etc.)	TELEPHONE NO.
Francis E. Ray, Jr. (SKIP)	DuPont Merck	508-671-8242

ROUTING	
NAME/SYMBOL	INT

SUBJECT: Amendment to Lic. No: 20-00320-17MA. → No 17?

SUMMARY

I need Actual labels to consider the amendment application.

He will be receiving them on Friday 9/25/92 by Fed. Exp.
He will send them to me sometime on the week of 9/28/92.

ACTION REQUIRED

Actual labels for Amendment.

NAME OF PERSON DOCUMENTING CONVERSATION	SIGNATURE	DATE
DIMITRIADIS		09/24/92

ACTION TAKEN

SIGNATURE	TITLE	DATE

116768

The Du Pont Merck Pharmaceutical Company
Radiopharmaceutical Division
331 Treble Cove Road
N. Billerica, MA 01862
(508) 667 9531

June 19, 1992

030-10796

United States Nuclear Regulatory Commission
Region I
Attn: Francis M. Costello, Chief
Research, Development & Decommissioning Section
Division of Radiation Safety and Safeguards
475 Allendale Road
King of Prussia, PA 19406

DU PONT
MERCK

Reference: Materials License No. 20-00320-17MA

Gentlemen:

This is a request for an amendment to the above-referenced license to authorize the use of our new company name on the labeling, packaging and package insert for the reagent kit Neurolite™.

Log
Remitter E. I. Du Pont Pharmaceuticals & Co.
Check No. 442744
Amount $ 310
Fee Category 3D
Type of Fee AMD
Date Check Rec'd 6/19/92
Date Completed 6/22/92
By

I have enclosed for your review a copy of...

the revised package insert,
the kit box label,
the kit's Vial A label, and
the kit's Vial B label.

The "Caution, Radioactive Material" label that is applied to the neck of the vial of the final preparation has not changed since the original submission of this label to your records on January 28, 1988.

As a result of data being generated from the clinical trials under IND 30,612 the package insert needs some revision. From the standpoint of radiation safety, the only significant modification needed in the insert since the original submission in 1988 is the increase in the range of activity of radioactive material specified for the diagnostic use of this product. The suggested dose range has been specified in this revised insert at 5-45 millicuries. The maximum dose is 45 mCi if the patient voids within 2 hours after the injection. A voiding interval of 4.8 hours allows for a maximum of 20 mCi to be administered. In the insert submitted to your office in 1988 the maximum dose range for intravenous administration was 5-20 millicuries.

A check is enclosed in the amount of $310.00 in payment of the amendment processing fee as specified for Fee Category 3D in the regulations of Title 10 CFR Part 170 Section 170.31.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy, Jr.

Francis E. Roy, Jr.
Health Physicist

JUN -2 AM 11:11
REGION I
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MAILING

116768

OFFICIAL RECORD COPY ML 10

JUN 22 1992

March 1992

The DuPont Merck Pharmaceutical Company
331 Treble Cove Road
Billerica, Massachusetts 01862

NEUROLITE®
Kit for the Preparation of Technetium Tc99m Bicisate for Diagnostic Use

DESCRIPTION: This kit formulation consists of two vials: Vial A contains Bicisate dihydrochloride (N, N'-1, 2-ethylenediylbis-L-cysteine diethyl ester dihydrochloride) and a reducing agent as a lyophilized solid, and Vial B contains a buffer solution. Each vial is sterile, non-pyrogenic and contains:

Vial A -

Bicisate dihydrochloride (ECD•2HCl)	0.90mg
Stannous chloride, dihydrate	0.072mg
Disodium EDTA, dihydrate	0.36mg
Mannitol	24 mg

Vial A is lyophilized and stored under nitrogen. The pH of the solution before lyophilization is 2.45 - 2.55. This vial is stored at room temperature (15-30°C).

Vial B -

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

Vial B is stored under air. The pH of the vial is 7.2 - 8.0. This vial is stored at room temperature (15-30°C).

This drug is administered by intravenous injection for diagnostic use after reconstitution with Sodium Pertechnetate Tc99m Injection. The precise structure of the Technetium complex is [N, N'-ethylendi-L-cysteinato(3-)]oxo[Tc99m] technetium (V), diethyl ester.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours[1]. Photons that are useful for the detection and imaging studies are listed in Table 1.

Table 1. Principle Radiation Emission Data

Radiation	Mean % / 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 Pb. A range of values for the relative attenuation of the radiation emitted by this radionuclide that results from interposition of various thicknesses of lead (Pb) is shown in Table 2. To facilitate control of the radiation exposure from MBq (mCi) amounts of this radionuclide, the use of a 0.25cm thickness of lead (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 time intervals after the time of calibration are shown in Table 3.

Table 3. Physical Decay Chart; Technetium Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fractions Remaining
0*	1.000	7	.447
1	.891	8	.398
2	.794	9	.355
3	.708	10	.316
4	.631	11	.282
5	.562	12	.251
6	.501		

*Calibration Time

CLINICAL PHARMACOLOGY: Technetium Tc99m Bicisate ([N, N'-ethylendi-L-cysteinato(3-)]oxo[Tc99m] technetium (V), diethyl ester) is well extracted by the monkey brain (4.7% I.D.) and is retained for a prolonged period post-injection ($T_{1/2}$ >24 hrs.) in the monkey brain. Autoradiographic studies of monkey brain show Technetium Tc99m Bicisate to be distributed according to regional cerebral blood flow in a pattern consistent with the standard tracer, ^{14}C iodoantipyrine.

The retention of Technetium Tc99m Bicisate in the CNS appears to be related to the relatively rapid metabolism of the parent compound in the brain. To date, the evidence for this is indirect. But, in monkey brain homogenates, the complex is metabolized completely to a single less lipophilic component. The same metabolite was present in the cerebrospinal fluid of a monkey dosed intravenously with Tc99m Bicisate. Imaging and/or biodistribution studies in eight diverse species show prolonged retention of the agent only in the brains of the primate species. Finally, imaging of the metabolite of Tc99m Bicisate demonstrates the inability of this material to cross the blood-brain barrier, suggesting that if it is formed in the brain, the metabolite can not cross the blood-brain barrier in either direction.

The major organs in humans that retain Tc99m Bicisate or its metabolite are the brain, gallbladder, kidneys and liver. There is initial uptake in the lungs but this activity clears quickly. The initial brain uptake in humans is about 6% of the injected dose. Its half-life is about 27 hours.

The primary route of excretion of Tc99m Bicisate is the urinary tract. On average, 84% of the injected dose is cleared through the bladder during the first 24 hours post injection with up to 50% of the injected dose cleared within the first two hours. Approximately 11% of the injected dose is cleared through the G.I. tract over 48 hours.

INDICATIONS AND USAGE: Technetium Tc99m Bicisate may be useful for the determination of regional patterns of blood perfusion in the brain.

CONTRAINDICATIONS: None known.

WARNINGS: None known.

PRECAUTIONS: Patients should be encouraged to ingest fluids and to void frequently during the 2-6 hours immediately post injection in order to minimize radiation dose to the bladder.

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 preparative procedure.

GENERAL

Radioactive drugs must be handled with care and appropriate safety measures should be used 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 Tc99m 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.

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.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long-term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc99m Bicisate affects fertility in males or females. Neurolite and its active ingredient bicisate dihydrochloride were tested in a battery of seven mutagenicity assays. Neurolite caused increases in unscheduled DNA synthesis in rat hepatocytes and sister chromatid exchanges in CHO cells in vitro. Neurolite did not cause gene mutations in the Salmonella/Ames and CHO/HPRT tests, nor did it cause chromosome aberrations in human lymphocytes in vitro. Bicisate dihydrochloride caused a borderline mutagenic response at the highest concentration of 5mg/plate in one out or four Salmonella test strains in the Ames assay. However, bicisate dihydrochloride did not show any mutagenic activity in the mouse micronucleus assay in vivo at doses up to 25mg/kg intravenously (>14000 times the maximum dose).

Pregnancy Category C

Animal reproduction and teratogenicity 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 reproductive capacity. There have been no studies in pregnant women.

Ideally, examinations using radiopharmaceuticals, especially those elective in nature, of a woman of childbearing capability, should be performed during the first few (approximately 10) days following the onset of menses.

Nursing Mothers

Technetium Tc99m 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 been established.

ADVERSE REACTIONS: In over 600 subjects, there were 4 cases of parosmia, all involving normal volunteers, at one site, who each reported a transient, mild, pleasant aromatic odor immediately after administration of Technetium Tc99m Bicisate. These were the only adverse events which were regarded as possibly related to the investigational drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Bicisate have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for intravenous administration, after preparation with fresh oxidant-free sodium pertechnetate Tc99m injection, in the average patient (70kg) is:

185-1665MBq (5-45mCi).

If the patient voids within 2 hours after the injection, a maximum of 1665MBq (45mCi) can be administered. A voiding interval of 4.8 hours allows for a maximum of 740MBq (20mCi) to be administered.

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 reconstitution, both Vial A and Vial B are to be stored at room temperature (15-30°C).

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

RADIATION DOSIMETRY: The radiation doses to organs and tissues of an average patient (70kg) per 1665MBq (45mCi) of Technetium Tc99m BICISATE injected intravenously are shown in Table 4.

Table 4. Radiation Absorbed Doses From Tc99m BICISATE

	Estimated Absorbed Radiation Dose[2]			
	mGy/1665 MBq (rads/45 mCi)		mGy/740 MBq (rads/20 mCi)	
Organ	2.0 Hr. Void		4.8 Hr. Void	
Brain	9.2	(0.9)	4.0	(0.4)
Gallbladder Wall	40.9	(4.1)	18.2	(1.8)
Lower Large Intestine Wall	21.2	(2.1)	11.1	(1.1)
Small Intestine	15.7	(1.6)	7.5	(0.8)
Upper Large Intestine Wall	27.4	(2.7)	12.4	(1.2)
Kidneys	12.1	(1.2)	5.3	(0.5)
Liver	8.8	(0.9	4.0	(0.4)
Lungs	3.4	(0.3)	1.3	(0.1)
Ovaries	9.9	(1.0)	5.7	(0.6)
Red Marrow	3.9	(0.4)	1.7	(0.2)
Bone Surfaces	5.8	(0.6)	2.6	(0.3)
Testes	3.6	(0.4)	2.6	(0.3)
Thyroid	5.8	(0.6)	2.6	(0.3)
Urinary Bladder Wall	49.5	(4.9)	53.7	(5.4)
Total Body	4.0	(0.4)	2.2	(0.2)

[2]Dosimetry calculated using the MIRD program at Oak Ridge Associated Universities.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m BICISATE

Preparation of the Technetium Tc99m Bicisate from the Kit for the Preparation of Technetium Tc99m Bicisate is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m injection to vial B, 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 (100mCi) sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection, in approximately 2.0 mL, to vial B.

e. With a sterile syringe, rapidly inject 3.0 mL of Sodium Chloride Injection into vial A to dissolve the contents. Shake the contents of the vial for a few seconds.

f. With another sterile syringe, immediately (within 30 seconds) transfer 1.0 mL of vial A to vial B.

g. Swirl the contents of the vial for a few seconds, and allow this mixture to stand for thirty minutes at room temperature.

h. Examine the vial contents for particulates and discoloration prior to injection.

i. Aseptically withdraw the required dose using a sterile shielded syringe. Use within six hours of preparation.

j. Radiochemical purity should be checked prior to patient administration.

DETERMINATION OF RADIOCHEMICAL PURITY

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

MATERIALS FOR TLC PROCEDURE

Baker-Flex silica gel IBF, 2.5 x 7.5 cm, Baker #2-4463
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 of the final solution by the thin layer chromatography (TLC) using Baker-Flex silica gel IBF plates and a solvent system of ethyl acetate.

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.

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 guage 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.

The plate is then placed in the pre-equilibrated TLC tank and developed to the 7.0 cm line (about 15 minutes). The plate is removed and dried in a ventilated area.

Quantification

Cut the TLC plate 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 Tc99m Bicisate and the bottom portion contains all radioimpurities.

Calculate the radiochemical purity using the following equation:

$$\%\ \text{Tc99m Bicisate} = \frac{\text{Activity on top portion}}{\text{Activity on Top + Bottom}} \times 100$$

Criteria

Tc99m Bicisate has an Rf of 0.9 +/- 0.1; Colloid, TcO_4^-, Tc99m $EDTA^-$ and Tc(IV) ECDremain at the origin. If the radiochemical purity is less than 90%, do not use the kit and discard the preparation.

HOW SUPPLIED: Du Pont's Kit for the Preparation of Technetium Tc99m Bicisate is supplied in kits of 10 vials, five (5) vials of A and five (5) vials of B. Included in each kit is one (1) package insert and ten (10) radiation labels.

Both Vial A and Vial B are stored at room temperature (15-30°C).

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

This reagent kit is supplied under IND #30,612 or other appropriate clinical research license. This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.200, 10 CFR Part 35 or under equivalent licenses of Agreement States.

Supplied By

The DuPont Merck Pharmaceutical Company
331 Treble Cove Road
Billerica, Massachusetts 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 508-667-9531)

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511916
See Product Monograph for dosage information and agent preparation directions. Use only additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

Neurolite®

Kit for the preparation of Technetium Tc99m Bicisate

Contents: 5 vials of Vial A each containing:
Bicisate Dihydrochloride (ECD•2HCl) - 0.90mg Mannitol - 24mg
Na_2 EDTA•$2H_2O$ - 0.36mg $SnCl_2$•$2H_2O$ - 0.072mg
Lyophilized and stored under nitrogen.
Contents: 5 vials of Vial B each containing:
Na_2HPO_4•$7H_2O$ - 4.1mg NaH_2PO_4•H_2O - 0.46mg
In 1ml Aqueous Solution.
Store at room temperature (15-30°C).
CAUTION: New drug limited by Federal (USA) law to investigational use.

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The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

DU PONT
PHARMA

Lot No.:

511914

See Product Monograph for dosage information.

Neurolite® Vial A

Kit for the preparation of Technetium Tc99m Bicisate

Contents: Bicisate Dihydrochloride (ECD•2HCl) - 0.90mg
$SnCl_2 \cdot 2H_2O$ - 0.072mg
$Na_2EDTA \cdot 2H_2O$ - 0.36mg
Mannitol - 24mg

CAUTION: New drug limited by Federal (USA) law to investigational use.

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Billerica, MA, USA 01962

Lot No.:

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ok w/?
B-3A

511915
Sodium Pertechnetate
Tc99m Injection
_____ MBq (mCi)

Time/Date Prepared

Neurolite® Vial B

Kit for the preparation of Technetium Tc99m Bicisate

Contents: In 1ml Aqueous Solution
$Na_2HPO_4 \cdot 7H_2O$ - 4.1mg
$NaH_2PO_4 \cdot H_2O$ - 0.46mg

See Product Monograph for dosage information.

CAUTION: New drug limited by Federal (USA) law to investigational use.

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BETWEEN:

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AND
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(FOR LFMS USE)
INFORMATION FROM LTS

PROGRAM CODE: 02512
STATUS CODE: 0
FEE CATEGORY: 3D
EXP. DATE: 19930630
FEE COMMENTS: _____
DECOM FIN ASSUR REQD: N

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
APPLICANT/LICENSEE: DU PONT MERCK PHARMACEUTICAL CO.
RECEIVED DATE: 920622
DOCKET NO: 3010796
CONTROL NO.: 116768
LICENSE NO.: 20-00320-17MA
ACTION TYPE: AMENDMENT

2. FEE ATTACHED
AMOUNT: $310.00
CHECK NO.: 4083963

3. COMMENTS

SIGNED Rebecca F. Bacon
DATE 6/26/92

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE 03 IS ENTERED (Y))

1. FEE CATEGORY AND AMOUNT: 3D $310

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
AMENDMENT ✓
RENEWAL _____
LICENSE _____

3. OTHER _____
_____

SIGNED _____
DATE 6/26/92