SEP 27 1993

License No. 20-00320-17MA
Docket No. 030-10796
Control No. 118167

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

Dear Mr. Roy:

Please find enclosed the renewal of 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\L2000320.17A - 09/24/93

ML 10

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

Sincerely,

Original Signed By:
Duncan White

Duncan White
Nuclear Materials Safety Branch
Division of Radiation Safety
and Safeguards

Enclosures:
1. Amendment No. 20
2. Requirements for Materials Licensees

DRSS:RI
White/srb

9/21/93

NOTE TO DMB:

THE ATTACHED DOCUMENTS ARE TO BE PROCESSED AS ONE MATERIALS LICENSING PACKAGE.

LICENSE NUMBER: 20-11320-17MA

DOCKET NUMBER: 030-10796

CONTROL NUMBER: 118167

THIS SHEET MAY BE DISCARDED AFTER PROCESSING.

THANK YOU!

050104

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. 20

In accordance with letter dated May 28, 1993, Approval No. 20-00320-17MA is amended in its entirety 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.	"Glucoscan 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 (IND 28,333) (NDA 19-785)	G. Technetium 99m labeled Sestamibi
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, packaged, 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, October 6, 1992, November 2, 1992 and May 28, 1993.

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 Cove 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 September 30, 1998.

For the U.S. Nuclear Regulatory Commission

Date SEP 27 1993

By Original Signed By:
Duncan White

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

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

May 28, 1993

U.S. Nuclear Regulatory Commission
Region I
Attn: Elizabeth Ullrich
475 Allendale Road
King of Prussia, PA 19406

030-10796

DU PONT
MERCK

Reference: Materials License #20-00320-17MA

Dear Ms. Ullrich:

This is a request for renewal of the above-referenced license.

All the communications referenced in License Condition #2 continue to provide valid descriptions of the packaging and labeling of the licensed material. Therefore, I am submitting this license renewal request with reference to the previously submitted documents.

The following documents continue to represent our current program and are attached for your review:

1. Application dated January 28, 1988.
2. Letter dated April 21, 1988.
3. Letter dated December 7, 1990.
4. Letter dated March 13, 1991.
5. Letter dated January 15, 1992.
6. Letter dated June 19, 1992.
7. Letter dated October 6, 1992.
8. Letter dated November 2, 1992.

A check is enclosed in the amount of $540 in payment of the license renewal fee as specified for Fee Category 3D in the regulations of Title 10 CFR Part 170, §170.31.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy Jr. (Skip)
Development Health Physicist

Telephone: 508-671-8242

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

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JUN 1 1993

JUL 0 2 1993

Docket No. 030-10796
License No. 20-00320-17MA
Control No. 118167

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

Dear Mr. Roy:

Subject: LICENSE RENEWAL APPLICATION

This is to acknowledge receipt of your application for renewal of material(s) license identified above. Your application is deemed timely filed, and accordingly, the license will not expire until final action has been taken by this office.

Any correspondence regarding the renewal application should reference the control number specified above.

Sincerely,

Original Signed By:

Sheryl Villar, Chief
Licensing Assistance Section
Division of Radiation Safety
and Safeguards

(15)
(5) 7/2/93 7/2/93

S:\PENDING\DUPONT.DTL OFFICIAL RECORD COPY June 22, 1993

ML 10

Radiopharmaceuticals Division
331 Treble Cove Road
N. Billerica, MA 01862
(508) 667 9531

File

November 2, 1992

DU PONT
MERCK

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

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

Gentlemen:

This is a request for license amendment for the above-referenced distribution approval.

The Food and Drug Administration has approved our kit Cardiolite® for a new indication, the diagnosis and localization of ischemia and coronary artery disease.

Attached is a copy of the FDA's approval of the supplemental new drug application (NDA) and a copy of the revised package insert. All other packaging and labeling for this product will remain the same as previously submitted to your office.

A check is enclosed in the amount of $330.00 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.
Development Health Physicist

PAYMENT QUESTIONS SHOULD BE DIRECTED TO THE PURCHASING SITE

E.I. DU PONT DE NEMOURS AND COMPANY

FINANCE - VENDOR PAYMENT
WILMINGTON, DELAWARE 19898

ALWAYS REFER TO OUR P.O. NUMBER IN YOUR CORRESPONDENCE

002343820 50313821 10/05/92

VOUCHER NO.	INVOICE NO.	P.O. NO.	DATE	GROSS	DISCOUNT	NET
KB4035	92492	YDMI2021	09-24-92	330.00	.00	330.00
			TOTALS	330.00	.00	330.00

DU PONT

E.I. DU PONT DE NEMOURS AND COMPANY
FINANCE - VENDOR PAYMENT
WILMINGTON, DELAWARE 19898

62-20
311

DATE	CHECK NUMBER	AMOUNT
10/05/92	50313821	$*********330.00

NOT VALID AFTER 90 DAYS

PAY TO THE ORDER OF
US GOVT
OFFICE OF THE CONTROLLER
US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

M. Shapiro

TO:
CITIBANK DELAWARE
A Subsidiary of Citicorp
One Penn's Way
New Castle, DE 19720

P121

⑈50313821⑈ ⑆031100207⑆ 3878857?⑈

Better Things for Better Living . . . from Du Pont

3. Store the reac[illegible] containing the Technetium Tc99m Sestamibi at 15-25°C prior to use. [illegible]ma the product should be aseptically withdrawn. Technetium Tc[illegible] Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Product should be used within 6 hours after preparation.

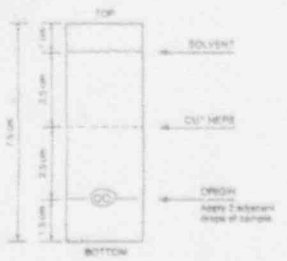
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

DETERMINATION OF RADIOCHEMICAL PURITY IN
Technetium Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5cm × 7.5cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1ml syringe with a 22-28 gauge needle, 1.5cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol* to a depth of 3-4mm. Cover the tank and let it equilibrate for ~10 minutes.
6. Develop the plate in the covered TLC Tank in ethanol* for a distance of 5cm from the point of application.
7. Cut the TLC plate 4cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc99m Sestamibi as:

$$\% \text{ Tc99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

TLC Plate Diagram



*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped in a cool dry place.

HOW SUPPLIED: Du Pont Radiopharmaceutical's CARDIOLITE® Kit for the Preparation of Technetium Tc99m Sestamibi is supplied as a 5ml vial in kits of two (2), five (5) and thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vials are lyophilized and stored under nitrogen. Store at 15-25°C before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each two (2) vial kit are one (1) package insert, six (6) vial shield labels and six (6) radiation warning labels. Included in each five (5) vial kit are one (1) package insert, six (6) vial shield labels and six (6) radiation warning labels. Included in each thirty (30) vial kit are one (1) package insert, thirty (30) vial shield labels and thirty (30) radiation warning labels.

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 Title 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.

DU PONT
PHARMA

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
For ordering Tel. Toll Free: 800-225-1572
All other business: 800-362-2666
(For Massachusetts and International, call 508-667-9531)

513092

Printed in U.S.A.

September 1992

U.S.A.
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

CARDIOLITE®

Kit for the Preparation of
Technetium Tc99m Sestamibi

FOR DIAGNOSTIC USE

DESCRIPTION: Each 5ml vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg
Sodium Citrate Dihydrate - 2.6mg
L-Cysteine Hydrochloride Monohydrate - 1.0mg
Mannitol - 20mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025mg
Stannous Chloride, Dihydrate, ($SnCl_2 \cdot 2H_2O$) - 0.075mg
Tin Chloride (Stannous and Stannic) Dihydrate, maximum (as $SnCl_4 \cdot 2H_2O$) - 0.066mg

Prior to lyophilization the pH is adjusted with HCl to 5.3-5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0-6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $Tc99m(MIBI)_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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-h (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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabecquerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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, Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	0.398
1	0.891	9	0.355
2	0.794	10	0.316
3	0.708	11	0.282
4	0.631	12	0.251
5	0.562		
6	0.501		
7	0.447		

*Calibration time

CLINICAL PHARMACOLOGY: Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of Thallous Chloride Tl-201. Scintigraphic images obtained in animals and man after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl-201 in normal and abnormal myocardial tissue.

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest, and clears with a $t_{1/2}$ of 1.8 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc99m Sestamibi in plasma.The myocardial biological half-life is approximately six hours after a rest or exercise injection. The biological half-life for the liver is approximately 30 minutes after a rest or exercise injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 30 minutes, after a rest or exercise injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than Thallous Chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose at rest and 1.5% of the injected dose at exercise. The following table illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

(Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects at rest and 5 subjects during exercise).

	Rest				Stress			
	Heart		Liver		Heart		Liver	
Time	Biological	Effective	Biological	Effective	Biological	Effective	Biological	Effective
5 mins	1.2	1.2	19.6	19.4	1.5	1.5	5.9	5.8
30 mins	1.1	1.0	12.2	11.5	1.4	1.3	4.5	4.2
1 hour	1.0	0.9	5.6	5.0	1.4	1.2	2.4	2.1
2 hours	1.0	0.8	2.2	1.7	1.2	1.0	0.9	0.7
4 hours	0.8	0.5	0.7	0.4	1.0	0.6	0.3	0.2

INDICATIONS AND USAGE: CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in the evaluation of ischemic heart disease. CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is useful in distinguishing normal from abnormal myocardium and in the localization of the abnormality, in patients with suspected myocardial infarction, ischemic heart disease or coronary artery disease. Evaluation of ischemic heart disease or coronary artery disease is accomplished using rest and stress techniques.

CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is also useful in the evaluation of myocardial function using the first pass technique.

Rest-exercise imaging with Tc99m Sestamibi in conjunction with other diagnostic information may be used to evaluate ischemic heart disease and its localization.

In clinical trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated apex, localization in the anterior or inferior-posterior wall in patients with suspected angina pectoris or coronary artery disease was shown. Disease localization isolated to the apex has not been established. Tc99m Sestamibi has not been studied or evaluated in other cardiac diseases.

It is usually not possible to differentiate recent from old myocardial infarction or to differentiate recent myocardial infarction from ischemia.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Infrequently, death has occurred 4 to 24 hours after Tc99m Sestamibi use and is usually associated with exercise stress testing (See Precautions).

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after 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.

Stress testing should be performed only under the supervision of a qualified physician and in a laboratory equipped with appropriate resuscitation and support apparatus.

The most frequent exercise stress test endpoints, which resulted in termination of the test during controlled Tc99m Sestamibi studies (two-thirds were cardiac patients) were:

Fatigue	35%
Dyspnea	17%
Chest Pain	16%
ST-depression	7%
Arrhythmia	1%

Carcinogenesis, Mutagenesis, Impairment of Fertility

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5rads/30mCi at rest, 1.2 rads/30mCi at exercise) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability. (See Dosimetry subsection in DOSAGE AND ADMINISTRATION section.)

The active intermediate, $[Cu(MIBI)_4]BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all in vitro). At cytotoxic concentrations (≥20µg/ml), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. $[Cu(MIBI)_4]BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9mg/kg, > 600 × maximal human dose).

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Sestamibi should be given to a pregnant woman only if clearly needed.

Nursing Mothers

Technetium Tc99m Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. 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: During clinical trials, approximately 8% of patients experienced a transient metallic or bitter taste immediately after the injection of Technetium Tc99m Sestamibi. A low cases of transient headache, flushing and non-itching rash have also been attributed to administration of this agent. Cases of angina, chest pain, and death have occurred (See Warnings and Precautions). The following adverse reactions have been rarely reported: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis in a wrist joint; and severe hypersensitivity, which was characterized by dyspnea, hypotension, bradycardia, asthenia and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration in a single dose to be employed in the average patient (70kg) is:

STD-1110MBq (10-30mCi)

The dose administered should be the lowest required to provide an adequate study consistent with ALARA principles (see also PRECAUTIONS).

When used in the diagnosis of myocardial infarction, imaging should be completed within four hours of administration (see also CLINICAL PHARMACOLOGY).

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.

Store at 15-25°C before and after reconstitution.

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

Table 4. Radiation Absorbed Doses from Tc99m Sestamibi

	Estimated Radiation Absorbed Dose			
	REST			
	2.0 hour void		4.8 hour void	
Organ	rads/30mCi	mGy/1110MBq	rads/30mCi	mGy/1110MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.5	5.6
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.9	0.5	4.8

	Estimated Radiation Absorbed Dose			
	STRESS			
	2.0 hour void		4.8 hour void	
Organ	rads/30mCi	mGy/1110MBq	rads/30mCi	mGy/1110MBq
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Small Intestine	2.4	24.4	2.4	24.4
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	32.2	3.3	32.2
Stomach Wall	0.5	5.3	0.5	5.2
Heart Wall	0.5	5.6	0.5	5.3
Kidneys	1.7	16.7	1.7	16.7
Liver	0.4	4.2	0.4	4.1
Lungs	0.3	2.6	0.2	2.4
Bone Surfaces	0.5	6.2	0.6	6.0
Thyroid	0.3	2.7	0.2	2.4
Ovaries	1.2	12.7	1.3	13.3
Testes	0.3	3.1	0.3	3.4
Red Marrow	0.5	4.5	0.5	4.4
Urinary Bladder Wall	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2

Radiopharmaceutical Internal Dose Information Center, July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831, (615) 576-3449.

INSTRUCTIONS FOR PREPARATION OF Technelite Tc99m Sestamibi

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

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the vial in a suitable radiation shield with a lined radiation cap.

d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection (925-5550MBq, (25-150mCi)) in approximately 1 to 3ml.

e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

f. Swirl the contents of the vial for a few seconds.

g. Remove the vial from the lead shield and place upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.

h. Remove the vial from the water bath, place in the lead shield and allow to cool for 15 minutes.

i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.

j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc99m concentration, post volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-785/S-002

SEP - 9 1992

The Du Pont Merck Pharmaceutical Company
331 Treble Cove Road
N. Billerica, Massachusetts 01862

Attention: Robert Kirsch
Associate Director, Regulatory Affairs

Dear Mr. Kirsch:

Reference is made to your supplemental new drug application (NDA) dated February 11, 1991, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardiolite (Kit for the preparation of Technetium, Tc99m Sestamibi).

This supplemental application provides for the indication; diagnosis and localization of ischemia and coronary artery disease.

We also acknowledge receipt of your amendments dated April 22, 1991 and August 6, 1992. The latter provides draft labeling in response to the Agency's supplement approvable letter dated July 27, 1992.

Additionally, we refer to our telephone conversation on September 3, 1992, in which you agreed to the following labeling revisions:

1. The INDICATIONS AND USAGE section will be revised to read as follows:

"CARDIOLITE, Kit for the preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in the evaluation of ischemic heart disease. CARDIOLITE, Kit for the preparation of Technetium Tc99m Sestamibi is useful in distinguishing normal from abnormal myocardium and in the localization of the abnormality, in patients with suspected myocardial infarction, ischemic heart disease or coronary artery disease. Evaluation of ischemic heart disease or coronary artery disease is accomplished using rest and stress techniques.

CARDIOLITE, Kit for the preparation of Technetium Tc99m Sestamibi, is also useful in the evaluation of myocardial function using the first pass technique.

Rest-exercise imaging with Tc99m Sestamibi in conjunction with other diagnostic information may be used to evaluate ischemic heart disease and its localization.

In clinical trials, using a template consisting of the anterior wall, inferior-posterior wall and isolated apex, localization in the anterior or inferior-posterior wall in patients with suspected angina pectoris or coronary artery disease was shown. Disease localization isolated to the apex has not been established. Tc99m Sestamibi has not been studied or evaluated in other cardiac diseases."

It is usually not possible to differentiate recent from old myocardial infarction or to differentiate recent myocardial infarction from ischemia."

2. The last paragraph in the General subsection of the PRECAUTIONS section will be deleted.

3. The ADVERSE REACTIONS section will be revised to read as follows:

"During clinical trials, approximately 8% of patients experienced a transient metallic or bitter taste immediately after the injection of Technetium Tc99m Sestamibi. A few cases of transient headache, flushing and non-itching rash have also been attributed to administration of the agent. Cases of angina, chest pain, and death have occurred (See WARNINGS and PRECAUTIONS). The following adverse reactions have been rarely reported: signs and symptoms consistent with seizure occurring shortly after administration of the agent; transient arthritis in the wrist joint; and severe hypersensitivity, which was characterized by dyspnea, hypotension, bradycardia, asthenia and vomiting within two hours after a second injection of Technetium Tc99m Sestamibi."

We also refer to the September 9, 1992, telephone conversation between yourself and Kathryn Huntley, of this Division, during which it was agreed that the following statement would be removed from the PRECAUTIONS section, Pregnancy subsection, to bring the labeling into conformance with 21 CFR 201.57:

"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."

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate the drug product is safe and effective

for use as recommended in the draft labeling dated August 6, 1992, as revised above by the September 3 and 9, 1992, telephone conversations. Accordingly, the supplemental application, with the labeling revisions described above, is approved effective as of the date of this letter.

These revisions are terms of the supplement approval. Marketing the product before making, exactly as agreed to, the revisions in the product's final printed labeling (FPL) may render the product misbranded and an unapproved new drug.

Please submit twelve (12) copies of the FPL identical to the draft labeling, with the agreed upon revisions, to the Food and Drug Administration (FDA) as soon as available. Seven of the copies should be individually mounted on heavy weight paper or similar material. The submission should be designated for administrative purposes as "FPL for Approved "NDA 19-785/S-002". Approval of this submission by the FDA is not required before the labeling is used.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Should there be any questions regarding this communication, please contact Ms. Susan Lange at (301) 443-5973.

Sincerely,

Wiley A. Chambers, M.D.
Acting Director
Division of Medical Imaging,
Surgical and Dental Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

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 116758
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.

March 1992

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 - 2.95. 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.

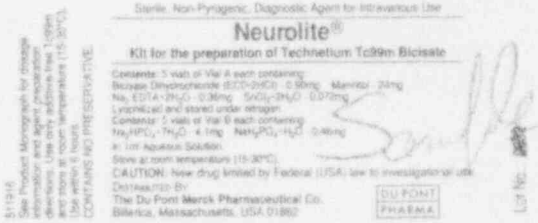
PHYSICAL CHARACTERISTICS

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.

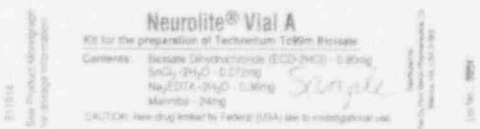
Table 1. Principle Radiation Emission Data

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

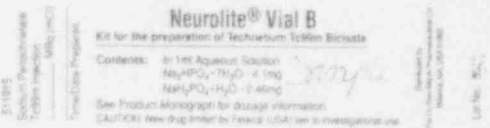
[1] Kocher, David C., "Radioactive Decay Data Tables", DOE/TIC 11026, 108 (1981).



KIT BOX LABEL



VIAL A LABEL



VIAL B LABEL

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

Sent certified mail
6/19/92 P-502-280-774

June 19, 1992

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™.

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

PAYMENT QUESTIONS SHOULD BE DIRECTED TO THE PURCHASING SITE

E.I. DU PONT DE NEMOURS AND COMPANY

FINANCE - VENDOR PAYMENT
WILMINGTON, DELAWARE 19898

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			TOTALS	310.00	.00	310.00

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E.I. DU PONT DE NEMOURS AND COMPANY

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WILMINGTON, DELAWARE 19898

64-1327
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US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

M. T. Shapiro
P121

TO: Wachovia Bank of Georgia, N.A.
Augusta, Georgia

⑈40810463⑈ ⑆061113279⑆ 07 519 318⑈

Better Things for Better Living . . . from Du Pont

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 - 2.95. 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).

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) ECD remain 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)

513059

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 F[illegible]al (USA) law to investigational use.

DISTRIBUTED BY
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.

Distributed by:
The DuPont Merck Pharmaceutical Co.
Billerica, MA, USA 01862

Lot No.:

Raum 3/24
ok w/?
B-3RA

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.

Distributed by:
The Du Pont Merck Pharmaceutical Co.
Billerica, MA, USA 01862

Lot No.:

Rawn 8/12/1 ok w/?

B-4AA

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

2080334952

January 15, 1992

Deliver C Front Seat
1/16/92 9:01 AM S. Coker

United States Nuclear Regulatory Commission
Region I
Attn.: John D. Kinneman, Chief
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 inserts for the reagent kits listed on this license.

I have enclosed for your review a copy of the package insert, the vial label, the lead shield label and the product boxes for the following kits:

"Cardiolite™" (NDA)
"Cardiolite™" (IND)
"DTPA"
"Glucoscan™"
"Hepatolite™"
"Microlite™"
"Osteolite™"
"Pulmolite™"
"Pyrolite™"

I have included color versions of the labeling for Cardiolite™ (NDA) and Pulmolite™. The color versions of the labeling for the other reagent kits are not yet available but will be printed the same way as the Cardiolite™ and Pulmolite™.

Since the kit Neurolite™ is still under development (IND 30,612), the labeling, packaging and insert have not yet been printed with the new company name. I will forward this material for your review as soon as I receive it from our Regulatory Affairs group.

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.

I also would like to follow-up with your office on the status of an amendment request for this license dated March 13, 1991 (see attached). This amendment was to specify the NDA for Cardiolite™ and a new manufacturer for our DTPA kit.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy, Jr.
Health Physicist
Telephone: (508) 671-8242

0222

THE DU PONT MERCK PHARMACEUTICAL COMPANY No. 801-00613

549 ALBANY ST., BOSTON, MA 02118

ALWAYS REFER TO OUR CHECK NUMBER IN YOUR CORRESPONDENCE

OUR NO.	VENDOR'S NO.	VENDOR'S DATE MO.	DAY	YR.	AMOUNT	DISCOUNT	FREIGHT	NET AMOUNT
		01	15	92	310.00			310.00

REMIT TO

DU PONT
MERCK

THE DU PONT MERCK PHARMACEUTICAL COMPANY No. 801-00613

BOSTON, MASSACHUSETTS

January 15, 1992

60-160
433

To the order of U.S. Nuclear Regulatory Commission

Pay **$310.00**

NOT GOOD FOR MORE THAN $10000.00

THE DU PONT MERCK PHARMACEUTICAL COMPANY
CASHIER ACCOUNT NO. 801

TO MELLON BANK N.A.
PITTSBURGH, PENNSYLVANIA

Helen F. McKeever

⑈801006 13⑈ ⑆043301601⑆ 198⑈4259⑈

8vvv

THE DU PONT MERCK PHARMACEUTICAL COMPANY No. 801-00613

549 ALBANY ST., BOSTON, MA 02118

ALWAYS REFER TO OUR CHECK NUMBER IN YOUR CORRESPONDENCE

OUR NO.	VENDOR'S NO.	VENDOR'S DATE MO.	DAY	YR.	AMOUNT	DISCOUNT	FREIGHT	NET AMOUNT
		01	15	92	31000			310.00

REMIT TO

DU PONT
MERCK

THE DU PONT MERCK PHARMACEUTICAL COMPANY No. 801-00613

BOSTON, MASSACHUSETTS

January 15, 1992

60-160
433

To the order of U.S. Nuclear Regulatory Commission

Pay **$310.00**

NOT GOOD FOR MORE THAN $10000.00

THE DU PONT MERCK PHARMACEUTICAL COMPANY
CASHIER ACCOUNT NO. 801

TO MELLON BANK N.A.
PITTSBURGH, PENNSYLVANIA

Helen F. McKeever

"801006 13" :043301601: 198-4259"

HOW SUPPLIED: Du Pont Radiopharmaceutical's CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is supplied as a 5ml vial in kits of two (2), five (5) and thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vials are lyophilized and stored under nitrogen. Store at 15-25°C before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each two (2) vial kit are one (1) package insert, six (6) vial shield labels and six (6) radiation warning labels. Included in each five (5) vial kit are one (1) package insert, six (6) vial shield labels and six (6) radiation warning labels. Included in each thirty (30) vial kit are one (1) package insert, thirty (30) vial shield labels and thirty (30) radiation warning labels.

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 Title 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.

November 1991

U.S.A.
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

CARDIOLITE®

Kit for the Preparation of Technetium Tc99m Sestamibi

FOR DIAGNOSTIC USE

DESCRIPTION: Each 5ml vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg
Sodium Citrate Dihydrate - 2.6mg
L-Cysteine Hydrochloride Monohydrate - 1.0mg
Mannitol - 20mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) - 0.025mg
Stannous Chloride, Dihydrate, ($SnCl_2 \cdot 2H_2O$) - 0.075mg
Tin Chloride (Stannous and Stannic) Dihydrate, maximum
(as $SnCl_2 \cdot 2H_2O$) - 0.086mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0-6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $Tc99m(MIBI)_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02

DU PONT
PHARMA

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
For ordering Tel. Toll Free: 800-225-1572
All other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

511996

Printed in U.S.A.

March 1991

U.S.A.
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

CARDIOLITE®

Kit for the Preparation of Technetium Tc99m Sestamibi

FOR DIAGNOSTIC USE

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PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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; Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	8	0.398
1	0.891	9	0.355
2	0.794	10	0.316
3	0.708	11	0.282
4	0.631	12	0.251
5	0.562		
6	0.501		
7	0.447		

*Calibration time

CLINICAL PHARMACOLOGY: Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of Thallous Chloride Tl-201. Scintigraphic images obtained in animals and man after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl-201 in normal and abnormal myocardial tissue.

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $T_{1/2}$ of 4.3 minutes at rest. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc99m Sestamibi in plasma. The myocardial biological half-life is approximately six hours after a rest injection. The biological half-life for the liver is approximately 30 minutes after a rest injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 28 minutes, after a rest injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than Thallous Chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose. The following table illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

(Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects.)

Time	Heart		Liver	
	Biological	Effective	Biological	Effective
5 min.	1.2	1.2	20	20
30 min.	1.1	1.0	12	11.3
1 hour	1.0	0.9	5.8	5.0
2 hours	1.0	0.6	2.2	1.7
4 hours	0.8	0.5	0.7	0.4

INDICATIONS AND USAGE: CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium, and in the localization of the abnormality, in patients with suspected myocardial infarction.

CARDIOLITE®, Kit for the Preparation of Technetium Tc99m Sestamibi is also useful in the evaluation of myocardial function using the first pass technique.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after 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

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5rads/30mCi) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability. (See Dosimetry subsection in DOSAGE AND ADMINISTRATION section.)

The active intermediate, $[Cu(MIBI)_4]BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all *in vitro*). At cytotoxic concentrations (≥20µg/ml), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay $[Cu(MIBI)_4]BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9mg/kg, > 600 × maximal human dose).

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Sestamibi should be given to a pregnant woman only if clearly needed.

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 Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. 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: During clinical trials, approximately 8% of patients experienced a transient metallic or bitter taste immediately after the injection of Technetium Tc99m Sestamibi. A few cases of transient headache, flushing and non-itching rash have also been attributed to administration of the agent. One patient demonstrated signs and symptoms consistent with seizure 8 to 10 minutes after administration of the drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Sestamibi have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

370-1110MBq (10-30mCi)

The dose administered should be the lowest required to provide an adequate study consistent with ALARA principles (see also PRECAUTIONS).

When used in the diagnosis of myocardial infarction, imaging should be completed within four hours after administration (see also CLINICAL PHARMACOLOGY).

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.

Store at 15-25°C before and after reconstitution.

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

Table 4. Radiation Absorbed Doses from Tc99m Sestamibi

Estimated Radiation Absorbed Dose

REST

Organ	2.0 hour void		4.8 hour void	
	rads/30mCi	mGy/1110MBq	rads/30mCi	mGy/1110MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8

Stabin, M., July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831; (615)576-3449.

INSTRUCTIONS FOR PREPARATION OF Technetium Tc99m Sestamibi

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

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the vial in a suitable radiation shield with a lifted radiation cap.

d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection (925-5550MBq, [25-150mCi)] in approximately 1 to 3ml.

e. Aseptically add the Sodium Pertechnetate Tc99m injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

f. Swirl the contents of the vial for a few seconds.

g. Remove the vial from the lead shield and place upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.

h. Remove the vial from the water bath, place in the lead shield and allow to cool for 15 minutes.

i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.

j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.

k. Store the reaction vial containing the Technetium Tc99m Sestamibi at 15-25°C until use, at such time the product should be aseptically withdrawn. Technetium Tc99m Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Product should be used within 6 hours after preparation.

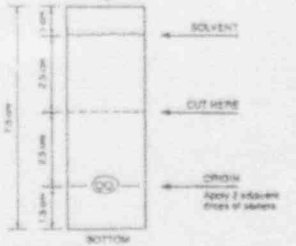
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

DETERMINATION OF RADIOCHEMICAL PURITY IN Technetium Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, precut to 2.5cm × 7.5cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1ml syringe with a 22-26 gauge needle, 1.5cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol* to a depth of 3-4mm. Cover the tank and let it equilibrate for ~10 minutes.
6. Develop the plate in the covered TLC Tank in ethanol* for a distance of 5cm from the point of application.
7. Cut the TLC plate 4cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc99m Sestamibi as:

$$\% \text{ Tc99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

TLC Plate Diagram



*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥95% ethanol content for one week after opening if stored tightly capped, in a cool dry place.

VIAL

Cardiolite®

Kit for the preparation of Technetium Tc99m Sestamibi

See package insert for full prescribing information.

Store at 15-25°C.

511997

DU PONT PHARMA

Marketed By
The Du Pont Merck
Pharmaceutical Company

Lot:

Exp.:

SHIELD

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal (U.S.A.) law
prohibits dispensing
without prescription.

MBq (mCi) Tc-99m/ml

Volume ml

Time/Date

Expiration Time Lot No.

Technetium Tc99m Sestamibi

Contents:

Sodium Pertechnetate Tc99m Injection

Tetrakis (2-methoxy isobutyl isonitrile)
Copper (I) tetrafluoroborate - 1.0mg

Stannous Chloride Dihydrate - 0.075mg

L-Cysteine Hydrochloride Monohydrate - 1.0mg

Sodium Citrate Dihydrate - 2.6mg

Mannitol - 20mg

Store: 15-25°C.

Use within 6 hours of reconstitution.

513002

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal (U.S.A.) law
prohibits dispensing
without prescription.

Technetium Tc99m Sestamibi

Contents:
Sodium Pertechnetate Tc99m Injection
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L-Cysteine Hydrochloride Monohydrate - 1.0mg
Sodium Citrate Dihydrate - 2.6mg
Mannitol - 20mg
Store: 15-25°C.
Use within 6 hours of reconstitution.

BOX

DU PONT
PHARMA

Cardiolite®

Kit for the preparation of Technetium Tc99m Sestamibi

CONTENTS AND STORAGE CONDITIONS:

1 Package Insert, 12 Radiation Labels and 2 Vials, each containing:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg
Stannous Chloride Dihydrate - 0.075mg
L-Cysteine Hydrochloride Monohydrate - 1.0mg
Sodium Citrate Dihydrate - 2.6mg
Mannitol - 20mg

Store at 15-25°C.

CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at 15-25°C. Use within 6 hours of reconstitution.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

517222

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Cardiolite®

Kit for the preparation of Technetium Tc99m Sestamibi

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

MARKETED BY

Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, MA. U.S.A. 01862

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Cardiolite®

Kit for the preparation of Technetium Tc99m Sestamibi

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS:
1 Package insert, 12 Radiation Labels and 5 Vials, each containing:
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg
Stannous Chloride Dihydrate - 0.075mg, L-Cysteine Hydrochloride Monohydrate - 1.0mg, Sodium Citrate Dihydrate - 2.6mg, Mannitol - 20mg
Store at 15-25°C.
CONTAINS NO PRESERVATIVE. See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at 15-25°C. Use within 6 hours of reconstitution.

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Kit for the preparation of Technetium Tc99m Sestamibi

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Kit for the preparation of Technetium Tc99m Sestamibi

USA/CANADA

March 1991

INVESTIGATIONAL MONOGRAPH

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

CARDIOLITE®
Kit for the preparation of
Technetium Tc99m Sestamibi
FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I)
tetrafluoroborate - 1.0mg
Stannous Chloride, Dihydrate,
($SnCl_2 \cdot 2H_20$) - 0.075mg
Sodium Citrate Dihydrate - 2.6mg
L-Cysteine Hydrochloride Monohydrate - 1.0mg
Mannitol - 20 mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

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 $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours (1). Photons that are useful for 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

(l) 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 lcm. 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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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; Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction 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	.5011		

*Calibration Time

CLINICAL PHARMACOLOGY: Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, analogous to Thallous Chloride Tl-201. Animal cross-over experiments using Tl-201 and Tc99m Sestamibi have confirmed that the myocardial distribution of Tc99m Sestamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man afte. the intravenous administration of Tc99m Sestamibi have been comparable to those obtained with Tl-201 in normal, ischemic and infarcted myocardial tissue.

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest and 1.6 minutes under exercise conditions. At five minutes post injection about 8% of the injected dose remains in circulation. The myocardial $t_{1/2}$ is approximately seven hours after either a rest or exercise injection. The $t_{1/2}$ for the liver is approximately 35 minutes after a rest or exercise injection. The ideal imaging time, reflecting the best compromise between heart count rate and contrast, is approximately 1-2 hours after a rest injection and 1/2 - 2 hours after an exercise injection. There is no evidence for change in myocardial distribution (redistribution), therefore imaging at delayed times is possible.

Myocardial uptake which is coronary flow dependent is 1.5% of the injected dose at exercise and 1.2% at rest. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited.

INDICATIONS AND USAGE: CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium, and in the localization of the abnormality, in patients with suspected myocardial infarction.

CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is also useful in the evaluation of myocardial function using the first-pass technique.

CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi may also be useful in conjunction with stress testing for the diagnosis and localization of ischemic heart disease.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

The Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

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 Sestamibi affects fertility in males or females. Several mutagenicity studies indicate that mutagenic changes are not likely to be induced by Technetium Tc99m Sestamibi.

Pregnancy

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m Sestamibi 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 Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. 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: Immediately after the injection of Technetium Tc99m Sestamibi, a small percentage (approximately 8%) of patients experienced a transient metallic or bitter taste. A few cases of transient headache, flushing and non-itching rash have also been attributed to administration of the agent. One patient demonstrated signs and symptoms consistent with seizure 8 to 10 minutes after administration of the drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Sestamibi have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

370-1110MBq (10-30mCi)

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.

Store at 15-25°C before and after reconstitution.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m Sestamibi

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

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.
c. Place the vial in a suitable radiation shield with a fitted radiation cap.
d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection [925-5550MBq (25-150mCi)] in approximately 1 to 3ml.
e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
f. Swirl the contents of the vial for a few seconds.
g. Remove the vial from the lead shield and place upright in a shielded boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.
h. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.
i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.

j. Assay the reaction vial using a suitable radioactivity calibration system and then complete and affix the "radioactive contents" label to the vial shield.

k. Aseptically withdraw material for use within six (6) hours. Store the reconstituted vial at 15-25°C. The vial contains no preservative.

DETERMINATION OF RADIOCHEMICAL PURITY IN TECHNETIUM Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5 cm x 7.5 cm.

2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.

3. Apply 1 drop of ethanol* using a 1 ml syringe with a 22-26 gauge needle, 1.5 cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.

4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).

5. The TLC tank is prepared by pouring ethanol* to a depth of 3-4mm. Cover the tank and let it equilibrate for ~ 10 minutes.

6. Develop the plate in the covered TLC TANK in ethanol* for a distance of 5 cm from the point of application.

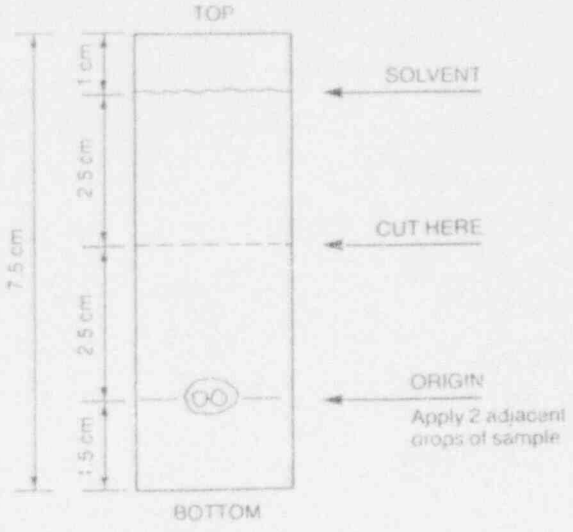
7. Cut the TLC plate 4 cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector.

8. Calculate the % Tc99m Sestamibi as:

$$\%\text{Tc99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

9. The dose should contain Tc99m Sestamibi $\geq$ 90%. Do not use if radiochemical purity is less than 90%.

TLC Plate Diagram



* The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99%) should remain at ≥ 95% ethanol content for one week after opening if stored tightly capped in a cool dry place.

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

Table 4. Radiation Absorbed Doses from Tc99m Sestamibi

	Estimated Radiation Absorbed Dose REST			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30 mCi	mGy/ 1110 MBq	rads/ 30 mCi	mGy/ 1110 MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8

	Estimated Radiation Absorbed Dose STRESS			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30 mCi	mGy/ 1110 MBq	rads/ 30 mCi	mGy/ 1110 MBq
Breasts	0.2	2.0	0.2	1.8
Gallbladder Wall	2.8	28.9	2.8	27.8
Small Intestine	2.4	24.4	2.4	24.4
Upper Large Intestine Wall	4.5	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	32.2	3.3	32.2
Stomach Wall	0.6	5.3	0.5	5.2
Heart Wall	0.5	5.6	0.5	5.3
Kidneys	1.7	16.7	1.7	16.7
Liver	0.4	4.2	0.4	4.1
Lungs	0.3	2.6	0.2	2.4
Bone Surfaces	0.6	6.2	0.6	6.0
Thyroid	0.3	2.7	0.2	2.4
Ovaries	1.2	12.2	1.3	13.3
Testes	0.3	3.1	0.3	3.4
Red Marrow	0.5	4.6	0.5	4.4
Urinary Bladder Wall	1.5	15.5	3.0	30.0
Total Body	0.4	4.2	0.4	4.2

Radiopharmaceutical Internal Dose Information Center, July 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831, (615) 576-3449.

HOW SUPPLIED: Du Pont Radiopharmaceutical's CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is supplied in kits of ten (10) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vial are lyophilized and stored under nitrogen. Store at 15-25°C before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each ten (10) vial kit are one (1) product monograph, twelve (12) vial shield labels and twelve (12) radiation warning labels.

This reagent kit is supplied under IND# 28-333 and/or Canadian pre-clinical NDS #RP-8607. This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to Sections 35.11 and 35.200, of Title 10 CFR Part 35, or under equivalent licenses of Agreement States.

Distributed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862
Tel: (508) 671-8357

Du Pont de Nemours (Deutschland) GmbH
Diagnostic Imaging Division Postfach 401240
Daimlerstrasse 23
D-6072 Dreieich, F.R. Germany
Tel: 49 (06103) 8030

511988

VIAL

511913
Sodium Pertechnetate
Tc99m Injection
____ MBq (mCi)

Time/Date Prepared

Cardiolite®

Kit for the preparation of Technetium Tc99m Sestamibi

Contents: Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg; Stannous Chloride Dihydrate - 0.075mg; L-Cysteine Hydrochloride Monohydrate - 1.0mg; Mannitol - 20mg

See Product Monograph for dosage information.

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

Distributed by:
The Du Pont Merck Pharmaceutical Co.
Billerica, MA, USA 01862

Lot No.:

dc 4/7

Rowan 9/20

13-1AA

SHIELD

511899

See Product Monograph for dosage information.
Reconstitute with additive-free Tc99m and store at 15-25°C. Use within 6 hours.
CONTAINS NO PRESERVATIVE

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

CARDIOLITE®

Kit for use in the preparation of Technetium Tc99m Sestamibi

CONTENTS
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg
Stannous Chloride Dihydrate - 0.075mg
L-Cysteine Hydrochloride Monohydrate - 1.0mg
Sodium Citrate Dihydrate - 2.6mg
Mannitol - 20mg
Lyophilized and stored under nitrogen.
Store at 15-25°C.

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

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

DU PONT
PHARMA

Lot No.

Vial shield labels, radiation warning labels, and a package insert are supplied in each carton.

STORAGE: Store the unreconstituted reaction vials at or below room temperature (2°C to 25°C). Store the reconstituted reaction vial at 2°C to 8°C in a suitable lead shield, and discard after 6 hours.

DIRECTIONS FOR PREPARATION

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding. Waterproof gloves should be worn during the preparation procedures.

To prepare Technetium Tc99m Pentetate Injection:

1. Prior to adding the sodium pertechnetate Tc99m solution to the vial, write the estimated amount of radioactivity to be added to the vial as well as the date and time of preparation in the spaces provided on the vial label. Then tear off a radiation warning label and attach it to the neck of the vial.
2. Remove the protective disc from a reaction vial and swab the rubber septum with an alcohol swab.
3. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 1/8 inch (3mm) and which has a fitted lead cap. Obtain 2 to 10mL of sterile, non-pyrogenic sodium pertechnetate Tc99m using a shielded syringe. The recommended maximum amount of Technetium Tc99m to be added to a reaction vial is 7.4 gigabecquerels (200mCi). Sodium pertechnetate Tc99m solutions containing an oxidizing agent are not suitable for use.
4. Using a shielded syringe, aseptically add the sodium pertechnetate Tc99m solution to the reaction vial while avoiding the buildup of excessive pressure in the vial. Pressure buildup may be avoided by injecting several milliliters of pertechnetate solution into the reaction vial, then withdrawing several milliliters of nitrogen gas (present to prevent oxidation of the complex) into the syringe. Repeat the procedure as necessary until the entire amount of the pertechnetate solution is added and normal pressure is established within the vial.
5. Place the lead cap on the vial shield and agitate the shielded vial until the contents are completely dissolved. To ensure maximum tagging, allow the preparation to stand for 15 minutes after mixing. Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.
6. Assay the product in a suitable calibrator, then record the radioassay information on the vial shield label, and affix it to the vial shield.
7. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the reaction vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made from the vial, replacement of the contents with air should be minimized.
8. The finished preparation should be discarded after 6 hours, or if used solely for the estimation of glomerular filtration rate, after 1 hour. It should be retained during its life in a lead vial shield with the lead cap in place.

NOTE: It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent Technetium Tc99m binding), and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded.

This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to sections 35.11 and 35.200 of Title 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and outside the United States, to persons authorized by the appropriate authority.

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Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
For ordering Tel: Toll-Free: 800-225-1572
All other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

Manufactured in Canada by:
Merck Frosst Canada, Inc.
Kirkland, Quebec, Canada

Printed in Canada 20196-0001

March 1991

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

DTPA

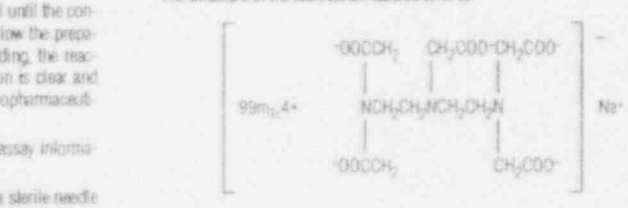
Kit for the Preparation of
Technetium Tc99m Pentetate Injection

DIAGNOSTIC
For Intravenous Use

DESCRIPTION: Each kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc99m Pentetate Injection for diagnostic use by intravenous injection.

Each 10mL reaction vial contains 25mg of pentetate calcium trisodium and not less than 0.25mg stannous chloride dihydrate and not more than 0.385mg total tin expressed as stannous chloride dihydrate in lyophilized form under an atmosphere of nitrogen. The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH range of the reconstituted radiopharmaceutical is 4 to 5. Addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc99m solution produces a rapid labeling which is essentially quantitative and which remains stable *in vitro* throughout the 6 hour life of the preparation. No bacteriostatic preservative is present.

The structure of the technetium labeled form is:



Its chemical name is:

Technetate (1-)^{99m}Tc, [*N*,*N*-bis[2-[bis(carboxymethyl)amino]ethyl]-glycinato (5-)]-, sodium

PHYSICAL CHARACTERISTICS

Technetium Tc99m 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 %/ 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 Technetium Tc99m is 0.78 R/mCi-hr at 1cm. The first half value layer is 0.017cm of lead. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 2.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness lead (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: Tc99m, 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: Following its intravenous administration, Technetium Tc99m Pentetate rapidly distributes itself throughout the extracellular fluid space from which it is promptly cleared from the body. The mechanism of excretion from the body is by glomerular filtration. There should be little or no binding of the chelate by the renal parenchyma. A variable percentage of the Technetium Tc99m Pentetate binds to the serum proteins; this ranges from 3.7% following a single injection to approximately 10% if the material is continuously infused. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance.

The images of the kidneys obtained in the first few minutes after administration of Technetium Tc99m Pentetate represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collection system and the renal pelvis.

Technetium Tc99m Pentetate tends to accumulate in intra-cranial lesions with excessive neovascularity or an altered blood-brain barrier. It does not accumulate in the choroid plexus.

INDICATIONS AND USAGE: Technetium Tc99m Pentetate Injection may be used to perform kidney imaging, brain imaging, to assess renal perfusion, and to estimate glomerular filtration rate.

CONTRAINDICATIONS: Hypersensitivity to any component of this product.

WARNINGS: None.

PRECAUTIONS:

GENERAL

The contents of the reaction vial before preparation are not radioactive. However, after the sodium pertechnetate Tc99m is added, adequate shielding of the final preparation must be maintained.

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc99m Pentetate Injection and are not to be administered directly to the patient.

The image quality may be adversely affected by impaired renal function.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to develop fully, and the possibility of missing certain lesions when imaging is restricted to the early period after injection should be borne in mind.

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

Technetium Tc99m Pentetate Injection should be formulated within six (6) hours prior to clinical use for brain and kidney imaging, and for assessing renal perfusion. For estimating glomerular filtration rates, Technetium Tc99m Pentetate Injection should be used within one (1) hour after formulation.

The components of the kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the sodium pertechnetate Tc99m solution and the withdrawal of doses for patient administration.

The Technetium Tc99m labeling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc99m solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc99m solutions containing oxidants should not be employed.

Technetium Tc99m Pentetate Injection as well as other radioactive drugs, must be handled with care, and appropriate safety measures should be taken to minimize radiation exposure to the patients consistent with proper patient management, and to minimize radiation exposure to clinical personnel.

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.

The preparation contains no bacteriostatic preservative. Therefore, after labeling with Technetium Tc99m, the solution should be stored at 2°C to 8°C in a suitable lead shield.

High background counts, poor images and erroneous clearance results have been observed with the use of vials exceeding the stated expiration time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc99m Pentetate Injection affects fertility in males or females. Mutagenicity studies have not been conducted.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Pentetate Injection. It is also not known whether Technetium Tc99m Pentetate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Pentetate Injection should be given to a pregnant woman only if clearly needed.

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 have not been established.

ADVERSE REACTIONS: Pyrogenic and allergic reactions to Technetium Tc99m Pentetate preparations have been reported in the literature.

DOSAGE AND ADMINISTRATION: The recommended dose range for intravenous administration, after reconstitution with oxidant-free sodium pertechnetate Tc99m, to be administered to the average patient (70kg) is:

Kidney imaging and glomerular filtration rate estimation . . . . . 111 to 185MBq (3 to 5mCi)

Brain imaging or assessment of renal perfusion . . . . . 370 to 740MBq (10 to 20mCi)

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Store finished preparation at 2°C to 8°C in a suitable lead shield.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution contains particulate matter or is not a clear solution.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to various organs of an average patient (70kg) from an intravenous injection of maximum doses of 185MBq (5mCi) and 740MBq (20mCi) of Technetium Tc99m Pentetate Injection are shown in Table 4.

Table 4. Estimated Absorbed Radiation Doses

Organs	Kidney Imaging or GFR Estimation		Brain Imaging or Assessment of Renal Perfusion	
	mGy/ 185MBq	rads/ 5mCi	mGy/ 740MBq	rads/ 20mCi
Kidneys	4.5	0.45	18.0	1.8
Whole Body	0.3	0.03	1.2	0.12
Bladder Wall				
2.0 hr void	5.75	0.58	23.0	2.3
4.8 hr void	13.5	1.35	54.0	5.4
Testes				
2.0 hr void	0.38	0.04	1.5	0.15
4.8 hr void	0.53	0.05	2.1	0.21
Ovaries				
2.0 hr void	0.55	0.06	2.2	0.22
4.8 hr void	0.78	0.08	3.1	0.31

[1]Method of calculation: "S" Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs. MIRD Pamphlet No. 11, 1975)

HOW SUPPLIED: Kit for the Preparation of Technetium Tc99m Pentetate Injection

Available in cartons containing 5 and 30 reaction vials, each reaction vial containing in lyophilized form, sterile and non-pyrogenic:

Pentetate Calcium Trisodium	25mg
Stannous Chloride Dihydrate (minimum)	0.25mg
(Maximum tin as stannous chloride dihydrate	0.385mg)

The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH of the reconstituted radiopharmaceutical is 4 to 5. The vials are sealed under an atmosphere of nitrogen.

VIAL

21803 0001
Tc 99m Activity _____
Time/Date Prepared _____
Recommended Adult Dose: 111-740MBq (3-20mCi). See package insert for dosage information. CONTAINS NO BACTERIOSTATIC PRESERVATIVE. FOR INTRAVENOUS USE ONLY AFTER LABELING WITH OXIDANT-FREE TECHNETIUM Tc 99m.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

DTPA

Kit for the Preparation of Technetium Tc 99m Pentetate Injection

CONTENTS & STORAGE CONDITIONS

Pentetate Calcium Trisodium - 25mg
Stannous Chloride Dihydrate (minimum) - 0.25mg
(Maximum tin as stannous chloride dihydrate - 0.385mg)

The pH of the reconstituted drug is 4-5. Sealed under nitrogen. After labeling with Technetium Tc 99m, store solution at 2°C-6°C in a suitable lead shield and use within time limits in package insert.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Lot. No:
Exp. Date:

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Billerica, MA, USA 01862

SHIELD

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m Pentetate Injection

After labeling with oxidant-free Technetium Tc 99m, store solution at 2°C-8°C in a suitable lead shield and use within time limits in package insert.

Usual adult dose: 111-740MBq (3-20mCi) of Technetium Tc 99m Pentetate Injection. See package insert for dosage information.

Total Activity MBq (mCi)

Activity Concentration MBq/ml (mCi/ml) Volume (ml)

Time / Date Prepared

Expiration Time Lot No.

986 0000

BOX

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DTPA

Kit for the Preparation of Technetium Tc99m Pentetate Injection

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Recommended Adult Dose: 111 to 740 megabecquerels (3 to 20 millicuries). Read enclosed package insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS: 1 Package Insert, 6 vial shield labels, 6 radiation warning labels, and 5 reaction vials each containing sterile and non-pyrogenic: Pentetate Calcium Trisodium - 25mg; Stannous Chloride Dihydrate (minimum) - 0.25mg; (Maximum tin as stannous chloride dihydrate - 0.385mg).

CONTAINS NO BACTERIOSTATIC PRESERVATIVE.
See Package Insert for dosage information. The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH range of the reconstituted radiopharmaceutical is 4 to 5. Sealed under nitrogen. After labeling with Technetium Tc99m, store solution at 2°C to 8°C in a suitable lead shield and use within time limits in package insert.

MARKETED BY
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, MA, U.S.A. 01862

MANUFACTURED IN CANADA BY
Merck Frosst Canada Inc.
Kirkland, Quebec, Canada

February 1991

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, MA, USA 01862

GLUCOSCAN®

Kit for the preparation of Technetium Tc99m Gluceptate

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Gluceptate Sodium - 200mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.14mg

Prior to lyophilization the pH is adjusted to between 8.5-9.1 with HCl and/or NaOH. The contents of the vial are lyophilized and contain no bacteriostatic preservative.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic oxidant-free Sodium Pertechnetate Tc99m Injection or isotonic saline.

The precise structure of stannous technetium-gluceptate complex is unknown at this time.

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. Principal 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 microcoloumbs/kg-MBq-hr (0.78R/mCi-hr) at 1 cm. 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	Fraction 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

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to organs and tissues of an average patient (70kg) from an intravenous injection of 740MBq (20mCi) of Technetium Tc99m Gluceptate are shown in Table 4.

Table 4. Radiation Absorbed Doses

Tissue	mGy/740MBq	(rads/20mCi)
Total Body	2.0	(0.2)
Renal Cortices	48.0	(4.8)
Kidneys	34.0	(3.4)
Liver	2.4	(0.24)
Bladder Wall		
2 Hour void	24.0	(2.4)
4.8 Hour void	56.0	(...6)
Ovaries		
2 Hour void	2.6	(0.26)
4.8 Hour void	4.0	(0.4)
Testes		
2 Hour void	1.6	(0.16)
4.8 Hour void	2.6	(0.26)

[2]Method of Calculation: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

HOW SUPPLIED: Du Pont Radiopharmaceutical's **GLUCOSCAN®** Kit for the preparation of Technetium Tc99m Gluceptate is supplied in kits of five (5) or thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted to between 8.5-9.1 with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized. Store at room temperature (15-30°C) before and after reconstitution. Technetium Tc99m Gluceptate contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

"This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.11 and 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States."

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Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Company
331 Treble Cove Road
Billerica, MA, USA 01862
For ordering Tel. Toll-Free: 800-225-1572
All other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

511913 Printed in U.S.A.

CLINICAL PHARMACOLOGY: Technetium Tc99m Gluceptate has been shown by comparative renograms to concentrate in the kidney by both glomerular filtration and tubular secretion. Kinetic studies have shown that while some of the activity is rapidly cleared through the urine, the remainder is retained in the renal cortex. Up to 15% of the injected dose is retained in the kidneys. The renal retention is greater in the cortex than in the medulla. The radiopharmaceutical may be bound to the proximal convoluted tubules which are located primarily in the renal cortex. In humans, about 25% of the injected dose is excreted in the urine during the first hour post-injection. Within the same interval, blood activity rapidly clears to less than 2% of the injected dose. In patients with renal disease, the blood clearance and urinary excretion of the drug are delayed.

The hepatobiliary system represents a normal alternate metabolic route of excretion for stannous gluceptate. Imaging studies in man have occasionally demonstrated hepatic uptake, gallbladder visualization, or intestinal activity.

Technetium Tc99m Gluceptate has also been shown to localize in areas of intracranial pathology characterized by a disturbance in the blood brain barrier. The mechanism is probably non-specific since neoplasms, cerebrovascular accidents, and extracerebral hematomas have all shown pronounced radionuclide uptake.

Used in conjunction with dynamic flow studies, Technetium Tc99m Gluceptate may detect vascular stenoses and arteriovenous malformations. There is no concentration of the agent in the salivary glands or the choroid plexus.

INDICATIONS AND USAGE: Technetium Tc99m Gluceptate is used for brain imaging. Technetium Tc99m Gluceptate is indicated for renal perfusion imaging as an adjunct in the diagnosis, localization, and evaluation of kidney disease. It may provide useful information about renal size, shape, and position and may delineate lesions affecting renal blood flow.

CONTRAINDICATIONS: None known.

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

PRECAUTIONS: Dehydration and/or patient positioning may result in failure to visualize urinary excretory structures in the presence of normal function. Adequate patient fluid intake and repositioning may reduce the incidence of such false positive studies.

The preparation contains no bacteriostatic preservative.

Technetium Tc99m Gluceptate should be used within six hours of preparation.

The Technetium Tc99m labeling reaction involved in preparing Technetium Tc99m Gluceptate depends on the maintenance of tin in the divalent state. Any oxidant present in the Sodium Pertechnetate Tc99m Injection employed may adversely affect the quality of the prepared agent. Thus, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used without first demonstrating that it is without adverse affect on the properties of the resulting agent.

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to develop fully and the possibility of missing certain lesions when imaging is restricted to the early period after injection should be borne in mind.

Image quality may be adversely affected by impaired renal function.

The use of Bacteriostatic Sodium Chloride Injection as a diluent for Sodium Pertechnetate Tc99m Injection may adversely affect the biologic distribution of the prepared agent, and its use is not recommended.

GENERAL

Contents of the vial are intended for reconstitution with Technetium Tc99m and are not to be administered directly to the patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

The 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 Gluceptate affects fertility in males or females.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Gluceptate. It is also not known whether Technetium Tc99m Gluceptate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Gluceptate should be given to pregnant women only if clearly needed.

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: Although infrequent, erythema has been reported in association with the use of Technetium Tc99m Gluceptate.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

Renal and Brain Imaging: 370-740MBq (10-20mCi).

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. Radiochemical purity should be checked prior to patient administration.

Optimal results for both renal and brain imaging are obtained one hour after administration. Studies have shown that although optimal target-to-background ratios for brain lesions are obtained at two hours post-injection, there is no improvement in diagnostic efficacy after one hour.

Store at room temperature (15-30°C) before and after reconstitution.

Parenteral drug products should be visually inspected for particulate matter and discoloration prior to administration, whenever solution and container permit.

INSTRUCTIONS FOR PREPARATION OF Technetium Tc99m Gluceptate: Preparation of Technetium Tc99m Gluceptate from the Kit for the preparation of Technetium Tc99m Gluceptate is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the 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 disk from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the reaction vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile, shielded syringe aseptically obtain 3-7ml [maximum 7.4GBq (200mCi)] of a suitable, oxidant-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection.

e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial.

f. Place the radiation shield cap on the vial shield and swirl the contents of the vial for one minute and let stand for 1-2 minutes.

g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.

h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to insure that it is free of particulate matter prior to injection.

i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.

j. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at room temperature (15-30°C). The vial contains no preservative.

VIAL

511920

Tc99m Activity

Time/Date Prepared
See package insert for dosage information.
Reconstitute with 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

Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

Contents and Storage Conditions
Gluceptate Sodium - 200mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.14mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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

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Lot No.:
Exp. Date:

C-1A

SHIELD

Technetium Tc99m Gluceptate

Contents

Gluceptate Sodium - 200mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.14mg
Use within 6 hours.

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511921

BOX

DU PONT
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Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

Sterile   Non-Pyrogenic

Diagnostic Agent for Intravenous Use

Lyophilized   5 Vials

517210

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The Du Pont Merck Pharmaceutical Co.
Billerica, MA, U.S.A. 01862

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Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

CONTENTS AND STORAGE CONDITIONS:
1 Package Insert, 12 Radiation Labels and 5 Vials, each containing:
Gluceptate Sodium - 200mg; Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.14mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

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Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

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Kit for the preparation of Technetium Tc99m Gluceptate

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BOX

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Glucoscan•

Kit for the preparation of
Technetium Tc99m Gluceptate

CONVENIENCE PACK

DU PONT
PHARMA

Glucoscan•

Kit for the preparation of
Technetium Tc99m
Gluceptate

Contents & Storage Conditions:

1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:

Gluceptate Sodium - 200mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum
($SnCl_2 \cdot 2H_2O$) - 0.14mg
The pH is adjusted with HCl
and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

DU PONT
PHARMA

Glucoscan•

Kit for the preparation of
Technetium Tc99m
Gluceptate

STERILE
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
inside bottom flap.

DU PONT
PHARMA

Glucoscan•

Kit for the preparation of
Technetium Tc99m
Gluceptate

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517211

DU PONT
PHARMA

Glucoscan•

Kit for the preparation of
Technetium Tc99m
Gluceptate

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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Open this end for Package Insert
and Radiation Labels.

Table 4. Estimated Radiation Absorbed Doses For Non-Jaundiced Patients

Organ	mGy/185MBq	(rads/5mCi)
Total Body	0.8	(0.08)
Liver	1.9	(0.19)
Gall Bladder Wall*	6.0	(0.6)
Small Intestine	11.0	(1.1)
Upper Large Intestine Wall	19.0	(1.9)
Lower Large Intestine Wall	14.0	(1.4)
Urinary Bladder Wall	4.6	(0.46)
Ovaries	4.1	(0.41)
Testes	0.3	(0.03)
Red Marrow	1.4	(0.14)

[2]Method of calculation: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs. MIRD Pamphlet No. 11 (1975).

*This value assumes that 80% of the activity localizes in the liver, and that 20% of the liver activity is transferred to the gallbladder.

Table 5. Estimated Radiation Absorbed Doses For Jaundiced Patients

Organ	mGy/296MBq	(rads/8mCi)
Total Body	1.2	(0.12)
Liver	5.0	(0.5)
Gall Bladder Wall	11.2	(1.12)
Small Intestine	13.0	(1.3)
Upper Large Intestine Wall	26.0	(2.6)
Lower Large Intestine Wall	18.0	(1.8)
Urinary Bladder Wall	7.0	(0.7)
Ovaries	6.0	(0.6)
Testes	0.5	(0.05)
Red Marrow	1.2	(0.12)

[3]Stabin, M., Calculations based on kinetic data for jaundiced patients with malignant obstructive disease, April 1989. Oak Ridge Assoc. Universities.

HOW SUPPLIED: DuPont Radiopharmaceutical's **HEPATOLITE®** Kit for the Preparation of Technetium Tc99m Disofenin is supplied as a set of five or thirty vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted to between 4-5 with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before and after reconstitution. Protect from light. The lyophilized drug product is light sensitive. Technetium Tc99m Disofenin contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

"This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Sections 35.11 and 35.200 of Title 10 CFR Part 35, or under equivalent licenses of Agreement States."

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Marketed By
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
For ordering Tel. Toll Free 800-225-1572
All other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

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Printed in U.S.A.

February 199

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, MA, USA 01862

HEPATOLITE®

Kit for the Preparation of Technetium Tc99m Disofenin

FOR DIAGNOSTIC USE

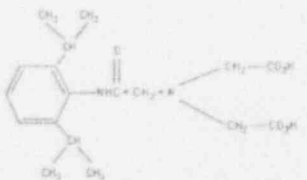
DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Disofenin - 20mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.2 mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.6mg

Prior to lyophilization the pH is adjusted to between 4-5 with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection.

The structure of disofenin is shown below:



The precise structure of stannous technetium-disofenin complex is unknown at this time.

PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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 emitted 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; Tc99m Half-Life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction 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: Disofenin (Hepatolite) is an iminodiacetic acid derivative with no known pharmacologic actions at the doses recommended.

Technetium Tc99m Disofenin is rapidly cleared from the circulation of normal individuals following intravenous administration; about 8% of the injected activity remains in the circulation 30 minutes post-injection. About 9% of the administered activity is excreted in the urine over the first two hours post-injection. The remainder of the activity is essentially quantitatively cleared through the hepatobiliary system. In fasting normal individuals, peak liver uptake occurs by 10 minutes post-injection and peak gallbladder accumulation by 30-40 minutes post-injection. Gallbladder visualization and visualization of intestinal activity occurs by 60 minutes post-injection in individuals with normal hepatobiliary function.

As the serum bilirubin level increases, the blood clearance becomes progressively delayed, resulting in higher background-to-liver radioactivity ratios. Kidney visualization becomes progressively prolonged compared with that in patients with normal biliary excretion. In patients with hepatocellular disease or partial biliary obstruction, there is delayed transit of the radiopharmaceutical to the gut.

INDICATIONS AND USAGE: Technetium Tc99m Disofenin is indicated as a hepatobiliary imaging agent. Hepatolite is indicated in the diagnosis of acute cholecystitis as well as to rule out the occurrence of acute cholecystitis in suspected patients with right upper quadrant pain, fever, jaundice, right upper quadrant tenderness and mass or rebound tenderness, but not limited to these signs and symptoms.

In otherwise healthy individuals, non-visualization of the gallbladder *4 hours* after administration of Hepatolite following a 2-6 hour fast and in the presence of activity in the small intestine is indicative of a diagnosis of acute cholecystitis. Under the same conditions in an otherwise healthy person, visualization of the gallbladder during a *1 hour* scintigraphy is effective in excluding a diagnosis of acute cholecystitis. If the gallbladder is not visualized by 1 hour, scanning must continue for four hours or until the gallbladder is visualized.

Cholescintigraphy is only partially effective in the diagnosis or excluding the diagnosis of acute cholecystitis in other conditions such as trauma, intercurrent disease, total parenteral nutrition (TPN) and nothing by mouth (NPO) status, all of which frequently result in false positive results (non-visualization). False negatives (visualization) are rarely seen in certain patients with cholelithiasis (myriad of small stones).

CONTRAINDICATIONS: None known.

WARNINGS: The possibility of allergic reactions should be considered.

PRECAUTIONS: The preparation contains no bacteriostatic preservative. Technetium Tc99m Disofenin should be used within six hours of preparation.

GENERAL

Contents of the vial are intended for reconstitution with Technetium Tc99m and are not to be administered directly to patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

The 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.

The technetium Tc99m labeling reactions involved in preparing the agent depend on maintaining the stannous ion in the reduced state. Any oxidant present in the sodium pertechnetate Tc99m solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc99m solution containing oxidants should not be employed.

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 Disofenin affects fertility in males or females.

Pregnancy Category C

Animal reproductive and teratogenicity studies have not been conducted with Technetium Tc99m Disofenin. It is also not known whether Technetium Tc99m Disofenin can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m should be given to a pregnant woman only if clearly needed.

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 feeding.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: Itching at the site of injection progressing to erythema multiforme has been reported following single administration. Rare cases of chills and nausea have been reported with related compounds.

DOSAGE AND ADMINISTRATION: The suggested dose range for i.v. administration, to be employed in the average patient (70kg) is:

Non-Jaundiced patient	37-185MBq (1-5mCi)
Patients with serum bilirubin level greater than 5mg/dl	111-296MBq (3-8mCi)

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration. (If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation *in situ*.) Do not backflush the syringe; slow injection is recommended. Radiochemical purity should be checked prior to patient administration.

Store at room temperature (15-30°C) before and after reconstitution.

The patient should be in a fasting state; 4 hours is preferable. False positives (non-visualization) may result if the gallbladder has been emptied by ingestion of food.

This preparation is usually administered to a patient only once. However, should a second dose be required, the interval between doses should not be less than 24 hours.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m DISOFENIN: Preparation of Technetium Tc99m Disofenin from Kit for the Preparation of Technetium Tc99m Disofenin is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the 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 central plastic disk from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the reaction vial in a suitable radiation shield with a fitted radiation shield cap.

d. With a sterile, shielded syringe, aseptically obtain and add to the reaction vial 4-5 ml of sterile, non-pyrogenic, additive-free Sodium Pertechnetate Tc99m Injection containing 444MBq to 3.7GBq (12 to 100mCi) of Tc99m. Note: If Sodium Pertechnetate Tc99m Injection must be diluted for use with Hepatolite, only preservative free sodium chloride injection, USP should be used. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution.

e. Place the radiation shield cap on the vial shield and swirl the contents of the vial for one minute and let stand for 4 minutes.

f. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.

g. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to insure that it is free of particulate matter and discoloration prior to injection.

h. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.

i. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at room temperature (15-30°C). The vial contains no preservative.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to organs and tissues of an average patient (70kg) from an intravenous injection of Technetium Tc99m Disofenin are shown in Tables 4 and 5.

VIAL

511923

Tc99m Activity

Time/Date Prepared

See package insert for dosage information. Reconstitute with 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

Hepatolite®

Kit for the preparation of Technetium Tc99m Disofenin

Contents and Storage Conditions

Disofenin - 20mg Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.24mg

Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.6mg

The pH is adjusted with HCl and/or NaOH.

Store at room temperature (15-30°C). Protect from light.

Lyophilized and stored under nitrogen.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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The Du Pont Merck Pharmaceutical Co.

Billerica, Massachusetts, USA 01862

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Lot No.:

Exp. Date:

C 2A

SHIELD

Technetium Tc99m Disofenin

Contents

Disofenin - 20mg

Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.24mg

Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.06mg

Use within 6 hours.

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511924

D-3A

BOX

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Hepatolite®

Kit for the preparation of Technetium Tc99m Disofenin

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Kit for the preparation of Technetium Tc99m Disofenin

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Kit for the preparation of Technetium Tc99m Disofenin

DU PONT
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Hepatolite®

Kit for the preparation of Technetium Tc99m Disofenin

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS:
1 Package Insert, 12 Radiation Labels and 5 Vials, each containing:
Disofenin - 20mg; Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.24mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C). Protect from light.
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

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Hepatolite®

Kit for the preparation of
Technetium Tc99m Disofenin

CONVENIENCE PACK

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Hepatolite®

Kit for the preparation of
Technetium Tc99m
Disofenin

Contents & Storage Conditions:
1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:
Disofenin - 20mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.24mg
Total Tin, maximum
($SnCl_2 \cdot 2H_2O$) - 0.6mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
Protect from light.
CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

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Hepatolite®

Kit for the preparation of
Technetium Tc99m
Disofenin

STERILE
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
inside bottom flap.

DU PONT
PHARMA

Hepatolite®

Kit for the preparation of
Technetium Tc99m
Disofenin

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517213

DU PONT
PHARMA

Hepatolite®

Kit for the preparation of
Technetium Tc99m
Disofenin

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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Open this end for Package Insert and Radiation Labels.

5. Remove the strip and allow it to air dry.
6. Cut the strip at the 1.9cm[1] line and measure each section for activity of Technetium Tc99m.
7. % free TcO_4^- = $\frac{\text{Net counts of top piece}}{\text{net counts of bottom piece + net counts of top piece}} \times 100$
8. The dose should contain no more than 10% of free pertechnetate at 30 to 60 minutes after reconstitution with sodium pertechnetate Tc99m.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to organs and tissues of an average patient (70kg) from an intravenous injection of 296MBq (8 mCi) of Technetium Tc99m Albumin Colloid are shown in Table 4.

Table 4. Radiation Doses*

Tissue	Radiation Absorbed Dose mGy/296MBq	(rads/8mCi)
Liver	27.2	(2.72)
Spleen	16.8	(1.68)
Red Marrow	2.2	(0.22)
Testes	0.1	(0.01)
Ovaries	0.45	(0.045)
Total body	1.5	(0.15)

[2]Method of Calculation: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).
*Assumes distribution, retention identical to Tc99m Sulfur Colloid.

HOW SUPPLIED: Du Pont Radiopharmaceutical's **MICROLITE®** Kit for the preparation of Technetium Tc99m Albumin Colloid is supplied in kits of five (5) or thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before reconstitution and store at 2-8°C after reconstitution. Protect from light. The lyophilized drug product is light sensitive. Technetium Tc99m Albumin Colloid contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

"This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.11 and 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States."

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The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, MA, USA 01862

MICROLITE®

Kit for the preparation of Technetium Tc99m Albumin Colloid

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Albumin Colloid -1 mg
Normal Human Serum Albumin - 19mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.0054mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg
Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg

MICROLITE®, Kit for the preparation of Technetium Tc99m Albumin Colloid is prepared from Albumin that was nonreactive when tested for hepatitis B antigen (HB_sAG).

Prior to lyophilization the pH is adjusted with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

The 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 stannous technetium-albumin colloid complex is unknown at this time.

PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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	Fraction 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: Following intravenous injection, Technetium Tc99m Albumin Colloid is cleared by reticuloendothelial (RE) cells which are distributed principally within the liver, spleen, and bone marrow. In the average normal patient, 80-90% of the cells of the RE system are located in the liver, 5-10% in the spleen and the remainder in the bone marrow. With progressive hepatic dysfunction, as in hepatic cirrhosis, a colloid shift occurs to the spleen, bone marrow and, eventually, the lungs. In clinical trials 7.0% ±3.6% of the injected activity was present in the blood at 15 minutes post-injection; with little change thereafter.

Concentration of activity in the liver and spleen of humans is essentially complete by 15 minutes after injection and remains constant for at least four hours thereafter. Clearance of activity through the urinary bladder occurs thereafter, so that between 4 and 30% of the administered activity is excreted by 24 hours post-injection.

Crossover imaging studies in normal and patient volunteers showed liver and spleen images entirely analagous to those obtained with sulfur colloid.

INDICATIONS AND USAGE: Technetium Tc99m Albumin Colloid is indicated for use as a diagnostic imaging agent for visualization of the functioning reticuloendothelial (RE) system: of the liver, spleen and bone marrow.

CONTRAINDICATIONS: Technetium Tc99m Albumin Colloid is contraindicated for persons with a history of hypersensitivity to products containing human serum albumin.

WARNINGS: The possibility of immediate hypersensitivity reactions must be considered with the use of this drug. Appropriate medical precautions should be taken, including the immediate availability of epinephrine, antihistamines, corticosteroid agents and advanced cardiopulmonary life support systems, in the event such a reaction occurs. **See ADVERSE REACTIONS.**

PRECAUTIONS: The labeling reactions involved in preparing the agent depend on maintaining tin in the reduced state. Any oxidant present in the Sodium Pertechnetate Tc99m Injection may thus adversely affect the quality of the prepared agent. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants, or other additions, should not be employed without first demonstrating that it is without adverse effect on the properties of the resulting agent.

The preparation contains no bacteriostatic preservative. Technetium Tc99m Albumin Colloid should be used within six hours of preparation.

General

Contents of the vial are intended for reconstitution with Technetium Tc99m and are not to be administered directly to the patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

The contents of the kit before preparation are not radioactive. However, after 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 Albumin Colloid affects fertility in males or females.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Albumin Colloid. It is also not known whether Technetium Tc99m Albumin Colloid can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m should be given to a pregnant woman only if clearly needed.

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 feeding.

Pediatric Use

Safety and effectiveness in children below the age of 18 have not been established.

ADVERSE REACTIONS: Hypersensitivity reactions, including anaphylaxis, have been reported in association with the use of Technetium Tc99m Albumin Colloid. Patients may not have demonstrated a previous reaction to drugs or blood products. A few deaths have occurred and several cases of pronounced changes in respiration, pulse and blood pressure have been reported. Other manifestations reported include urticaria, chills, fever, nausea, dizziness, flushing, cyanosis, abdominal pain, and diaphoresis. **See WARNINGS.**

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

37-296MBq (1-8 mCi)

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to patient administration.

Re-suspend colloid by repeated inversion of the shielded vial immediately prior to withdrawal of dose into syringe. Inspect the vial for foreign particulates. Do not administer if foreign particulates are found in the colloid. (If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation *in situ*.) Do not backflush the syringe. Do not use if clumping of the contents is observed. Slow injection is recommended and for optimum results imaging may begin about 15 minutes after injection. Radiochemical purity should be checked prior to patient administration, using the following or equivalent procedure.

The reconstituted vial of Microlite appears as a milky suspension.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

INSTRUCTIONS FOR PREPARATION OF Technetium Tc99m Albumin Colloid: Preparation of Technetium Tc99m Albumin Colloid from Kit for the preparation of Technetium Tc99m Albumin Colloid is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.
c. Place the reaction vial in a suitable radiation shield with a fitted radiation cap.
d. With a sterile, shielded syringe aseptically obtain 2-8ml [maximum 2.8GBq (75 mCi)] of a suitable, oxidant-free, sterile non-pyrogenic Sodium Pertechnetate Tc99m Injection.
e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial. Be sure to maintain a nitrogen atmosphere in the vial by not introducing air during reconstitution.
f. Place the radiation shield cap on the vial shield and swirl the contents of the vial for one minute and let stand for 1-2 minutes.
g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.
h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected for foreign particulates. Do not administer if foreign particulates are found in the colloid.
i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.
j. Prior to withdrawing an aliquot, and with the radiation shield and cap in place, resuspend the colloid by repeatedly inverting the vial for 15 seconds.
k. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at 2-8°C and protect from light. The vial contains no preservative.

DETERMINATION OF FREE PERTECHNETATE
IN TECHNETIUM Tc99m LABELED ALBUMIN COLLOID

1. Mark a 1 x 5cm Gelman ITLC-SG strip at 1.3cm from one end and 1.9cm from the other end with a pencil.
2. Place one ml of *fresh* methyl ethyl ketone into a glass vial.
3. Spot the preparation at the 1.3cm line and dry the spot with nitrogen.
4. Immediately place the strip into the vial and allow to develop in the capped vial until the solvent front reaches the top of the strip.

VIAL

511926

Tc99m Activity

Time/Date Prepared

See package insert for dosage information.
Reconstitute with additive-free Tc99m and store at 2-8°C. Use within 6 hours.

CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

Microlite®

Kit for the preparation of Technetium Tc99m Albumin Colloid

Contents and Storage Conditions

Albumin Colloid - 1mg Normal Human Serum Albumin - 10mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.0054mg Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg Sodium Phosphate (Anhydrous) - 10mg
Store at room temperature (15-30°C). Protect from light.
Lyophilized and stored under nitrogen.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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

DU PONT
PHARMA

Lot No.:
Exp. Date:

SHIELD

Technetium Tc99m Albumin Colloid

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

Contents

Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.0054mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg
Poloxamer 188 - 1.1mg; Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg
Use within 6 hours.

MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511927

D-4AA

BOX

DU PONT PHARMA

Microlite®

Kit for the preparation of Technetium Tc99m
Albumin Colloid

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

Lyophilized 5 Vials

517214

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The Du Pont Merck Pharmaceutical Co
Billerica, MA U.S.A. 01862

DU PONT PHARMA

Microlite®
Kit for the preparation of Technetium Tc99m
Albumin Colloid

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

DU PONT PHARMA

Microlite®
Kit for the preparation of Technetium Tc99m
Albumin Colloid

CONTENTS AND STORAGE CONDITIONS
1 Package Insert, 12 Radiation Labels and 5 Vials, each containing:
Albumin Colloid: 1mg; Normal Human Serum Albumin: 10mg; Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$): 0.095mg; Total Tin, maximum ($SnCl_2 \cdot 2H_2O$): 0.11mg; Poloxamer 188: 1.1mg; Medronate Disodium: 0.13mg; Sodium Phosphate (anhydrous): 10mg
Store at room temperature (15-30°C). Protect from light.
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at 2-8°C. Use within 6 hours.

DU PONT PHARMA

Microlite®
Kit for the preparation of Technetium Tc99m
Albumin Colloid

DU PONT PHARMA

Microlite®
Kit for the preparation of Technetium Tc99m
Albumin Colloid

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Microlite®

Kit for the preparation of
Technetium Tc99m Albumin Colloid

CONVENIENCE PACK

DU PONT
PHARMA

Microlite®

Kit for the preparation of
Technetium Tc99m
Albumin Colloid

Contents & Storage Conditions:
1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:
Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.0054mg
Total Tin, maximum
($SnCl_2 \cdot 2H_2O$) - 0.17mg
Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg
Store at room temperature (15-30°C).
Protect from light.
CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at 2-8°C. Use within 6 hours.

DU PONT
PHARMA

Microlite®

Kit for the preparation of
Technetium Tc99m
Albumin Colloid

STERILE
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

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

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
inside bottom flap.

DU PONT
PHARMA

Microlite®

Kit for the preparation of
Technetium Tc99m
Albumin Colloid

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517215

DU PONT
PHARMA

Microlite®

Kit for the preparation of
Technetium Tc99m
Albumin Colloid

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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

Open this end for Package Insert
and Radiation Labels.

February 1991

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

OSTEOLITE®

Kit for the Preparation of
Technetium Tc99m Medronate

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Medronate Disodium - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.6mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg

Prior to lyophilization, the pH is adjusted to between 7.0-7.5 with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

Administration is by intravenous injection for diagnostic use, after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection.

The precise structure of stannous technetium medronate complex is known at this time (JACS Vol. 102, 2476,1980).

PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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 (0.78 R/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 emitted by a factor of 1,000.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness lead (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: Tc99m, Half-life 6.02 Hours

Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	0.447
1	0.891	8	0.398
2	0.794	9	0.355
3	0.708	10	0.316
4	0.631	11	0.282
5	0.562	12	0.251
6	0.501		

*Calibration time

CLINICAL PHARMACOLOGY: During the initial twenty-four hours following intravenous injection of Technetium Tc99m Medronate, about 50% of the dose is retained in the skeleton, and about 50% is renally excreted; less than 2% of the injected dose remains in the vascular system. Blood levels fall to 3-5% of the injected dose by three hours post-injection.

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(For Massachusetts and International, call 508-667-9531)

511028

Printed in U.S.A.

Upon intravenous injection, osseous uptake of Technetium Tc99m Medronate appears to be related to bone metabolic activity and to skeletal blood flow. Technetium Tc99m Medronate exhibits a specific affinity for areas of altered osteogenesis.

INDICATIONS AND USAGE: Technetium Tc99m Medronate may be used as a bone imaging agent to delineate areas of altered osteogenesis.

CONTRAINDICATIONS: None known.

WARNINGS: This class of compounds is known to complex cations such as calcium. Particular caution should be used with patients who have, or who may be predisposed to, hypocalcemia (i.e., tetkalosis).

Preliminary reports indicate impairment of brain scans using Sodium Pertechnetate Tc99m Injection which have been preceded by a bone scan using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain scans. It is recommended, where feasible, that brain scans precede bone imaging procedures.

Alternatively, a brain imaging agent such as Technetium Tc99m Pentetate may be used.

PRECAUTIONS: To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake and to void as often as possible after the injection of Technetium Tc99m Medronate, and for 4 to 6 hours after the imaging procedure.

The preparation contains no bacteriostatic preservatives. Technetium Tc99m Medronate should be used within six hours of preparation.

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Medronate and are NOT to be administered directly to the patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

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 Medronate affects fertility in males or females.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Medronate. It is also not known whether Technetium Tc99m Medronate can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Medronate should be given to a pregnant woman only if clearly needed.

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 16 have not been established.

ADVERSE REACTIONS: Several cases of allergic dermatological reactions have been reported in association with the use of Osteolite. In addition, one case of cardiac arrest in a patient also undergoing pulmonary function testing one and one-half hours after the performance of an Osteolite scan has been reported.

Several reactions have also been reported in association with other radiopharmaceuticals of the diphosphonate class, particularly Technetium Tc99m Medronate. These are usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, chills, nausea, fever and vomiting.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

370 to 740 MBq (10-20mCi)

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.

Optimal imaging results are obtained 1-4 hours after administration. The image quality may be adversely affected by obesity, old age, and impaired renal function.

Store at room temperature (15-30°C) before and after reconstitution.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m MEDRONATE: Preparation of Technetium Tc99m Medronate from Kit for the Preparation of Technetium Tc99m Medronate is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the reaction vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile, shielded syringe, aseptically obtain 2-8ml [maximum 7.4 GBq (200mCi)] of a suitable, oxidant-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection.

e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial.

f. Place the radiation shield cap on the vial shield and swirl the contents of the vial for one minute and let stand for 1-2 minutes.

g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.

h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to insure that it is free of particulate matter prior to injection. Do not use if the solution is cloudy.

i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.

j. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at room temperature (15-30°C). The vial contains no preservative.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[2] to organs and tissues of an average patient (70kg) from an intravenous injection of 740 MBq (20mCi) of Technetium Tc99m Medronate are shown in Table 4.

Table 4. Radiation Absorbed Doses

Organ	Radiation (mGy/740 MBq)	Absorbed Dose (rads/20mCi)
Total Body	1.3	(0.13)
Bone Total	7.0	(0.70)
Red Marrow	5.6	(0.56)
Kidneys	8.0	(0.80)
Liver	0.6	(0.06)
Bladder wall		
2 hr void	26.0	(2.60)
4.8 hr void	62.0	(6.20)
Ovaries		
2 hr void	2.4	(0.24)
4.8 hr void	3.4	(0.34)
Testes		
2 hr void	1.6	(0.16)
4.8 hr void	2.2	(0.22)

[2]Method of calculation: "S," Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11, 1975.

HOW SUPPLIED: Du Pont Radiopharmaceutical's **OSTEOLITE®** Kit for use in the preparation of Technetium Tc99m Medronate is supplied in kits of five (5) or thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted to between 7.0-7.5 with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before and after reconstitution. Technetium Tc99m Medronate contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

"This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.11 and 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States."

VIAL

511929

Tc99m Activity

Time/Date Prepared
See package insert for dosage information.
Reconstitute with 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

Osteolite®

Kit for the preparation of Technetium Tc99m Medronate

Contents and Storage Conditions
Medronate Disodium - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.6mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
Lyophilized and stored under nitrogen.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

MARKETED BY
The DuPont Merck Pharmaceutical Co.
Billerica, MA, USA 01862

DU PONT
PHARMA

Lot No.:
Exp. Date:

C-41A

SHIELD

Technetium Tc99m Medronate

Contents

Medronate Disodium - 10mg

Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.6mg

Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg

Use within 6 hours.

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511930

BOX

DU PONT
PHARMA

Osteolite®

Kit for the preparation of Technetium Tc99m Medronate

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Osteolite®

Kit for the preparation of Technetium Tc99m Medronate

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Osteolite®

Kit for the preparation of Technetium Tc99m Medronate

DU PONT
PHARMA

Osteolite®

Kit for the preparation of Technetium Tc99m Medronate

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS:
1 Package Insert, 12 Radiation Labels and 5 Vials, each containing:
Medronate Disodium - 10mg; Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 1.5mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVES
See Package Insert for dosage information. Reconstitute with sterile, non-Tc99m and store at room temperature (15-30°C). Use within 8 hours.

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The Du Pont Merck Pharmaceutical Co.
Billerica, MA, U.S.A.

DU PONT
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Osteolite•

Kit for the preparation of Technetium Tc99m Medronate

CONVENIENCE PACK

DU PONT
PHARMA

Osteolite•

Kit for the preparation of Technetium Tc99m Medronate

Contents & Storage Conditions:
1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:

Medronate Disodium - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.6mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg
The pH is adjusted with: HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

DU PONT
PHARMA

Osteolite•

Kit for the preparation of Technetium Tc99m Medronate

STERILE
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels inside bottom flap.

DU PONT
PHARMA

Osteolite•

Kit for the preparation of Technetium Tc99m Medronate

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517217

DU PONT
PHARMA

Osteolite•

Kit for the preparation of Technetium Tc99m Medronate

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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Billerica, Massachusetts, USA 01862

Open this end for Package Insert and Radiation Labels

1

-4/1

In PEDIATRIC patients, the radiation absorbed doses using the maximum recommended dose for lung imaging are based on 1.85 MBq (50µCi) per kilogram of body weight (except in newborns where the maximum recommended dose of 18.5 MBq (500 µCi) is used and are shown in Table 6, which lists the maximum dosage for children from newborn to adults.

Table 7.
Pediatric Absorbed Radiation Dose
For Lung Imaging*

Age	Newborn	1 Year Old	5 Year Old	10 Year Old	15 Year Old
Weight (kg)	3.5	12.1	20.3	33.5	56.0
Maximum Recommended Dose MBq (mCi)	18.5 (0.5)	22.2 (0.6)	37 (1.0)	62.9 (1.7)	103.6 (2.8)
Absorbed Dose (mGy (rads)/max dose)					
Total Body	0.6 (0.06)	0.3 (0.03)	0.31 (0.031)	0.48 (0.048)	0.41 (0.041)
Lungs	19.0 (1.9)	4.6 (0.46)	5.8 (0.58)	8.7 (0.87)	7.7 (0.77)
Liver	1.4 (0.14)	0.9 (0.090)	0.62 (0.062)	1.8 (0.18)	1.2 (0.12)
Bladder Wall	2.1 (0.21)[1]	1.5 (0.15)[1]	3.1 (0.31)[1]	3.9 (0.39)[1]	4.1 (0.41)[1]
Ovaries	0.38 (0.038)	0.2 (0.02)	0.19 (0.019)	0.44 (0.044)	0.41 (0.041)
Testes	0.31 (0.031)	0.13 (0.013)	0.19 (0.019)	0.2 (0.02)	0.36 (0.036)

*2 hour voiding interval
[1] 4.8 hour voiding interval

Assumptions:
1. Used biologic data from Kaul et al., Berlin, 1973.
2. For the Newborn, 1 year old, and 5 year old, the "S" values calculated from the preliminary phantoms of ORNL were used. The 10 year old and 15 year old "S" values were taken from Heinrichs et al., Berlin, 1990.

Table 8. Absorbed Radiation Doses
The following table represents the absorbed radiation dose resulting from the intraperitoneal administration of 111 megabecquerels (3 millicuries) of Technetium Tc99m Albumin Aggregated.

Organ	Shunt Patency (Open)		Shunt Patency (Closed)	
	mGy	rem	mGy	rem
Lung	5.4	0.53	1.58	0.158
Ovaries	0.18	0.018	1.08	0.108
& Testes	to 0.30	to 0.030		
Organs in the				
Peritoneal Cavity	---	---	1.58	0.158
Total Body	0.35	0.035	0.57	0.057

Assumptions:
Calculations for the absorbed radiation dose are based upon an effective half-time of 2 hours for the open shunt and 6.02 hours for the closed shunt and an even distribution of the radiopharmaceutical in the peritoneal cavity with no biological clearance.

HOW SUPPLIED: Du Pont Radiopharmaceutical's **Pulmolite®** Kit for the Preparation of Technetium Tc99m Albumin Aggregated is supplied in kits of five (5) or thirty (30) vials, sterile and non-pyrogenic.

The contents of the vial are lyophilized and stored under sterile filtered air. Store at room temperature (15-30°C) before reconstitution. Protect from light. Store at 2-8°C after reconstitution. Technetium Tc99m Albumin Aggregated contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.11 and 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States.

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For ordering Tel. Toll Free: 800-225-1572
All other business: 800-362-2998
(For Massachusetts and International, call 508-667-9521)

Printed in U.S.A.

February 1991

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

PULMOLITE®

Kit for the Preparation of
Technetium Tc99m Albumin Aggregated

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Albumin Aggregated - 1.0mg
Albumin Human - 10mg
Stannous Chloride, Minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg
Total Tin, Maximum ($SnCl_2 \cdot 2H_2O$) - 0.15mg
Sodium Chloride - 10mg

The pH of the kit when reconstituted with 5ml of Sodium Chloride Injection is 5.0-8.0. The contents of the vial are lyophilized and stored under sterile filtered air.

The Albumin Human was non-reactive when tested for Hepatitis B surface antigen ($HBsAg$). The aggregated particles are formed by denaturation of Albumin Human in a heating and aggregation process. Each vial contains 3.6-6.5 million particles. By light microscopy, more than 90% of the particles are between 10 and 90 micrometers, while the typical average size is 15 to 30 micrometers; none is greater than 150 micrometers.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. No less than 90% of the pertechnetate Tc99m added to the vial is bound to the aggregates at preparation time and remains bound throughout the 6 hour lifetime of the preparation.

The precise structure of stannous technetium albumin aggregated complex is unknown at this time.

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. Principal 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 0.6 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

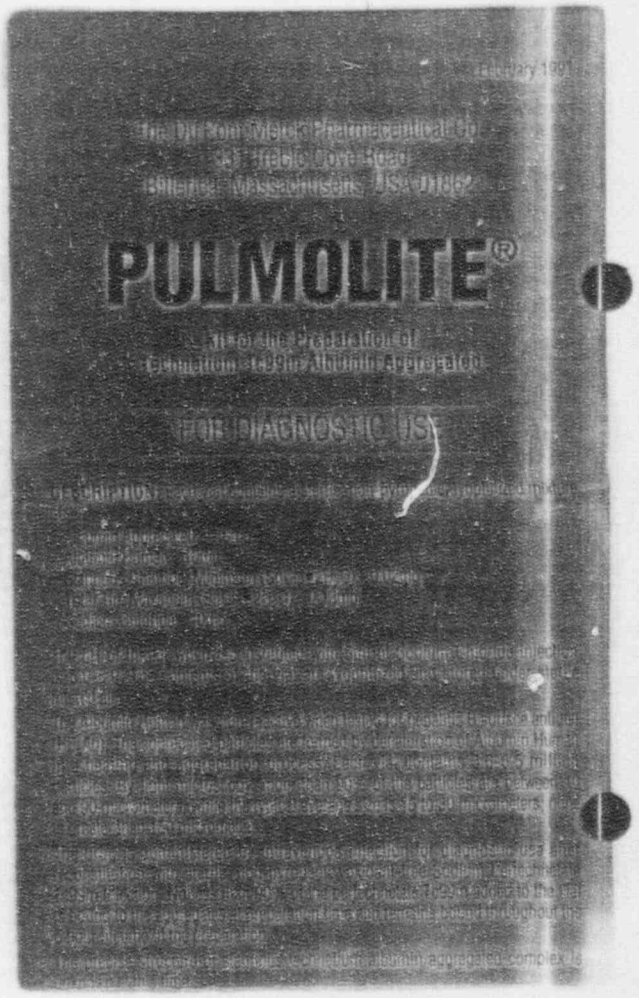
Shield Thickness (Pb) cm	Coefficient of Attenuation
0.017	0.5
0.08	10^{-1}
0.16	10^{-2}
0.25	10^{-3}
0.33	10^{-4}

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	Fraction 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: Immediately following intravenous injection, more than 80% of the Albumin Aggregated is trapped in the pulmonary alveolar capillary bed. The imaging procedure can thus be started as soon as the injection is complete. Assuming that a sufficient number of radioactive particles has been used, the distribution of radioactive aggregated particles in the normally perfused lung is uniform throughout the vascular bed, and will produce a uniform image. Areas of reduced perfusion will be revealed by a correspondingly decreased accumulation of the radioactive particles, and these areas are imaged as areas of decreased photon density.

Organ selectivity is a direct result of particle size. Below 1-10 micrometers the material is taken up by the reticuloendothelial system. Above 10 micrometers the aggregates become lodged in the lung capillaries by a purely mechanical process. Distribution of particles in the lungs is a function of regional pulmonary blood flow.

Lung to liver ratios greater than 20:1 are obtained in the first few minutes post-injection. Elimination of the Technetium Tc99m Albumin Aggregated from the lungs occurs with a half-life of about 5 hours. Cumulative urinary excretion studies show an average of 20% elimination of the injected Tc99m dose 24 hours post administration.

Following administration of Technetium Tc99m Albumin Aggregated by intraperitoneal injection, the radiopharmaceutical mixes with the peritoneal fluid. Clearance from the peritoneal cavity varies from insignificant, which may occur with complete shunt blockage, to very rapid clearance with subsequent transfer into the systemic circulation when the shunt is patent.

Serial images should be obtained of both the shunt and lung (target organ). However, an adequate evaluation of the difference between total blockage of the shunt and partial blockage may not be feasible in all cases.

INDICATIONS AND USAGE: Technetium Tc99m Albumin Aggregated Injection is a lung imaging agent which may be used as an adjunct in the evaluation of pulmonary perfusion in adults and children.

Technetium Tc99m Albumin Aggregated may be used in adults as an imaging agent to aid in the evaluation of peritoneo-venous (LeVeen) shunt patency.

CONTRAINDICATIONS: Technetium Tc99m Albumin Aggregated Injection should not be administered to patients with severe pulmonary hypertension.

The use of Technetium Tc99m Albumin Aggregated Injection is contraindicated in persons with a history of hypersensitivity reactions to products containing human serum albumin.

WARNINGS: Although adverse reactions specifically attributable to the Technetium Tc99m Albumin Aggregated have not been noted, the literature contains reports of deaths occurring after the administration of Albumin Aggregates to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or vasomotoric reactions to preparations of Technetium Tc99m Albumin Aggregated have been reported.

PRECAUTIONS: In patients with right-to-left cardiac shunt, additional risk may exist due to the rapid entry of Albumin Aggregated into the systemic circulation. The safety of this agent in such patients has not been established.

Hypersensitivity reactions are possible whenever protein-containing materials such as pentothrixate labeled Albumin Aggregated are used in man. Epinephrine, antihistamines, and corticosteroids should be kept available for immediate use.

The intravenous administration of any particulate material such as Albumin Aggregated imposes a temporary, small mechanical impediment to blood flow. While this effect is probably physiologically insignificant in most patients, the administration of Albumin Aggregated is potentially hazardous in acute cor pulmonale and other states of severely impaired pulmonary blood flow.

The preparation contains no bacteriostatic preservatives. Technetium Tc99m Albumin Aggregated Injection should be used within 6 hours of preparation.

Technetium Tc99m Albumin Aggregated Injection is physically unstable and consequently the particles settle with time. Failure to agitate the vial adequately before use may result in non-uniform distribution of radioactive particles.

Mix the contents of the syringe just before injection. If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation. Slow injection is recommended.

Do not use if clumping of the contents is observed.

The Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m injection containing oxidants should not be employed.

General

Contents of the vial are intended for reconstitution with Technetium Tc99m and are not to be administered directly to the patient.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

The 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 Albumin Aggregated Injection affects fertility in males or females.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Albumin Aggregated Injection. It is also not known whether Technetium Tc99m Albumin Aggregated Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Albumin Aggregated Injection should be given to a pregnant woman only if clearly needed.

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 feeding.

Pediatric Use

The lowest reasonable number of particles should be used in pediatric patients with right-to-left cardiac shunt, in neonates and in severe pulmonary disease.

ADVERSE REACTIONS: The literature contains reports of deaths occurring after the administration of Albumin Aggregates to patients with pre-existing severe pulmonary hypertension. Instances of hemodynamic or vasomotoric reactions to preparations of Technetium Tc99m Albumin Aggregated have been reported. (See Warnings)

DOSAGE AND ADMINISTRATION: The recommended intravenous dose range for the average (70kg) ADULT patient is 37MBq to 148MBq (1-4mCi) of Tc99m Albumin Aggregated after reconstitution with oxidant-free Sodium Pertechnetate Tc99m Injection. The recommended number of particles per single injection is 200,000-700,000, with the suggested number being approximately 350,000. Depending on the activity added and volume of the final reconstituted product, the volume of the dose may vary from 0.2 to 1.2ml. See Table 4 for adult dosing information.

The number of particles available per megabecquerel (millicurie) dose of Technetium Tc99m Albumin Aggregated Injection will vary depending on the physical decay of the technetium that has occurred. The number of particles available in any specific dose may be estimated by calculating the number of particles per millliter at the time of calibration.

In PEDIATRIC patients, the suggested intravenous doses employed for perfusion lung imaging are in the range of 0.925MBq to 1.85MBq per kilogram (25 to 50µCi/kg) of body weight with a usual dose of 1.11MBq per kilogram (30µCi/kg), except in newborns, in whom the administered dose should be 7.4 MBq to 18.5MBq (200-500µCi). A minimum dose of 7.4MBq (200µCi) should be employed for this procedure. The number of particles will vary with age and weight of the child as indicated in the pediatric dose information table below (see Table 5).

The suggested intraperitoneal dosage range used in the average patient (70kg) for peritoneo-venous (LeVeen) shunt patency evaluation is 37 to 111 megabecquerels (1 to 3 millicuries). Adequate measures should be taken to assure uniform mixing with peritoneal fluid. Serial images of both the shunt and target organ should be obtained and correlated with other clinical findings. Alternatively, the drug may be administered by percutaneous transtubal injection. The suggested percutaneous transtubal (within shunt limb) dosage range for the average patient (70kg) is 12 to 37 megabecquerels (0.3 to 1.0 millicurie) in a volume not to exceed 0.5ml.

Parenteral drug products should be inspected visually for foreign particulate matter and discoloration prior to administration whenever solution and container permit.

The reconstituted vial of Pulmolite appears as a milky suspension.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. Mix the contents of the vial by gentle inversion just prior to withdrawing a patient dose.

Radiochemical purity should be checked prior to patient administration.

Mix the contents of the syringe just before injection. If blood is drawn into the syringe, any unnecessary delay prior to injection may lead to clot formation. Slow injection is recommended.

Lung imaging may begin immediately after intravenous injection of the radiopharmaceutical.

Table 4. Particles Per Dose in Thousands (Adults)

Reconstitution Activity			Administered Dose	
MBq (mCi)	37MBq (1mCi)	74MBq (2mCi)	111MBq (3mCi)	148MBq (4mCi)
740 (20)	350	500		
1110 (30)	-	333	500	667
1480 (40)	-	250	375	500
1850 (50)	-	200	300	400

Table 5. Particles Per Dose in Thousands[1] (Pediatric)

AGE	Newborn	1 Year	5 Years	10 Years	15 Years
WEIGHT(kg)	3.5	12.1	20.3	33.5	55.0
USUAL ADMINISTERED DOSE MBq(mCi)	7.4(0.2)	13.4(0.4)	22.5(0.6)	37.1(1.0)	61.0(1.7)
RANGE OF PARTICLES ADMINISTERED	10-50	50-100	200-300	200-300	200-700

[1]Based on a dose of 7.4MBq (200µCi) for newborns and 1.11MBq (30µCi)/kg for other pediatric patients.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m ALBUMIN AGGREGATED

Preparation of Technetium Tc99m Albumin Aggregated Injection from the Kit by the preparation of Technetium Tc99m Albumin Aggregated is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m injection to the 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 on the neck of the vial.

b. Wear proof gloves should be worn during the preparation procedure. Remove the plastic disk from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the reaction vial in a suitable radiation shield with a fitted radiation cap.

d. With a sterile, shielded syringe, aseptically obtain 2-8ml (740-1850MBq (20-50mCi)) of a suitable, oxidant-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection.

e. Aseptically enter the vial septum with the needle at an oblique angle and add the Sodium Pertechnetate Tc99m Injection in such a way that it first strikes the vial wall.

f. Place the radiation shield cap on the vial shield and mix the contents of the vial by repeated gentle inversion until all the material is suspended. Avoid formation of foam.

g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.

h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to insure that the suspension is free of foreign matter before proceeding. Do not administer if foreign particulates are found in the preparation. To ensure maximum tagging, allow the preparation to stand for 1-2 minutes after mixing.

i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.

j. Prior to withdrawing an aliquot, resuspend the particles by repeatedly inverting the shielded vial for 15 seconds.

k. Aseptically withdraw material using a sterile shielded syringe with a vial-to-needle (18-21 gauge).

l. The finished preparation should be refrigerated at 2-8°C when not in use and discarded after 6 hours. The vial contains no bacteriostatic preservatives.

RADIATION DOSIMETRY

The estimated absorbed radiation dose(s) to an average ADULT patient (70kg) from an intravenous injection of 148MBq (4 millicuries) of Technetium Tc99m Albumin Aggregated Injection are shown in Table 6.

Table 6. Absorbed Radiation Dose

Tissue	mGy/148MBq	(rads/4mCi)
Total Body	0.60	(0.060)
Lungs	8.8	(0.88)
Liver	0.72	(0.072)
Spleen	0.68	(0.068)
Kidneys	0.44	(0.044)
Bladder Wall		
2 Hr void	1.2	(0.12)
4.8 Hr void	2.2	(0.22)
Testes		
2 Hr void	0.24	(0.024)
4.8 Hr void	0.26	(0.026)
Ovaries		
2 Hr void	0.30	(0.030)
4.8 Hr void	0.34	(0.034)

[1]Method of calculation: "S", Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

VIAL

511932

Tc99m Activity

Time/Date Prepared

See package insert for dosage information.
Reconstitute with additive-free Tc99m and store at 2-8°C. Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

Pulmolite®

Kit for the preparation of Technetium Tc99m Albumin Aggregated

Contents and Storage Conditions
Albumin Aggregated - 1.0mg Albumin Human - 10mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.13mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg
Sodium Chloride - 10mg
Store at room temperature (15-30°C). Protect from light.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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

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Lot No.:
Exp. Date:

C-5A

SHIELD

Technetium Tc99m Albumin Aggregated

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

Contents

Albumin Aggregated - 1.0mg Albumin Human - 10mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.13mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg
Sodium Chloride - 10mg
Use within 6 hours.

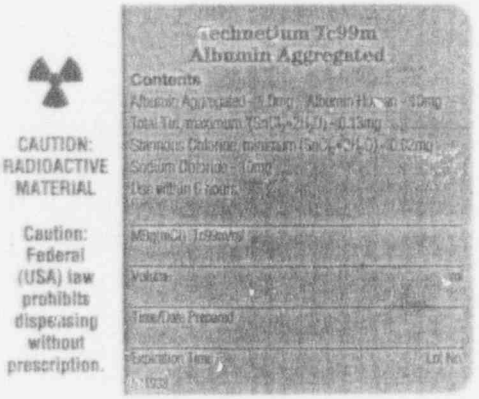
MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511933



BOX

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PHARMA

Pulmolite®

Kit for the preparation of Technetium Tc99m
Albumin Aggregated

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS:
1 Package Insert, 13 Radiation Labels and 5 Vials, each containing:
Albumin Aggregated - 1.0mg; Albumin Human - 10mg; Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg; Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.12mg; Sodium Chloride - 10mg

Store at room temperature (15-30°C). Protect from light.
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive-free Tc^{99m} and store at 2-8°C. Use within 6 hours.

MARKETED BY
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co
Billerica, MA, U.S.A. 01862

FA 22

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Kit for the preparation of Technetium Tc99m Albumin Aggregated

CONVENIENCE PACK

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Pulmolite®

i for the preparation of
Technetium Tc99m
Albumin Aggregated

ents & Storage Conditions:
'ackage Insert, 72 Radiation Labels
1 30 Vials, each containing
umin Aggregated - 1mg
umin Human - 10mg
nnous Chloride, minimum
$(SnCl_2 \cdot 2H_2O)$ - 0.02mg
al Tin, maximum
$(SnCl_2 \cdot 2H_2O)$ - 0.13mg
re at room temperature (15-30°C)
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Package Insert for dosage information.
onstitute with additive free Tc99m and
e at 2-8°C. Use within 6 hours.

DU PONT
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Pulmolite®

Kit for the preparation of
Technetium Tc99m
Albumin Aggregated

STF[illegible]
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
inside bottom flap.

DU PONT
PHARMA

Pulmolite®

Kit for the preparation of
Technetium Tc99m
Albumin Aggregated

← CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

← (maximum six vials)

517219

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Pulmolite®

Kit for the preparation of
Technetium Tc99m
Albumin Aggregated

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

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

Open this end for Package Insert
and Radiation Labels.

Table 4. Absorbed Radiation Dose Bone and Cardiac Imaging

Tissue	Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates mGy/740MBq	(rads/20mCi)
Skeleton*	10.8	(1.08)
Bone Marrow	7.6	(0.76)
Kidneys	9.4	(0.94)
Red Marrow	4.4	(0.44)
Total Body†	3.0	(0.30)
Bladder		
2 hour void	19.4	(1.94)
4.8 hour void	46.0	(4.60)
Testes		
2 hour void	2.0	(0.20)
4.8 hour void	3.0	(0.30)
Ovaries		
2 hour void	1.9	(0.19)
4.8 hour void	3.0	(0.30)
Heart		
Normal	1.5	(0.15)
Impaired	2.9	(0.29)

*Dose at point of highest uptake may be a factor of 10 higher.

†If patient voids frequently after radiopharmaceutical is administered, this dose will be reduced slightly.

Table 5. Absorbed Radiation Dose Blood Pool Imaging*‡

Tissue	Sodium Pertechnetate Tc99m 30 min. Post Injection with Sodium (Pyro- and Trimeta-) Pyrophosphate mGy/740MBq	(rads/20mCi)
Total Body	3.2	(0.32)
Spleen	3.6	(0.36)
Bladder Wall†	24.0	(2.40)
Testes	2.4	(0.24)
Ovaries	4.6	(0.46)
Blood	10.4	(1.04)

*Assume 75% of the Sodium Pertechnetate Tc99m remains labeled to red blood cells and the other 25% remains as pertechnetate.

†If 25% excreted with 1 hr. T_{biol}.

‡Method of calculation: A Schema for Absorbed-Dose Calculations for Biologically Distributed Radionuclides, Supplement No. 1, MIRD Pamphlet No. 1, p. 7, 1968.

HOW SUPPLIED: Du Pont Radiopharmaceutical's **PYROLITE®** Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates is supplied as a set of five or thirty vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is adjusted to between 4.5-5.5 with hydrochloric acid and/or sodium hydroxide solution. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before and after reconstitution. Contains no preservatives. Included in each five (5) vial kit is one (1) package insert and twelve (12) radiation labels. Included in each thirty (30) vial kit is one (1) package insert and seventy-two (72) radiation labels.

"This reagent kit is approved for use by persons licensed by the U.S. Nuclear Regulatory Commission pursuant to Section 35.11 and 35.200 of Title 10 CFR Part 35 or under equivalent licenses of Agreement States."

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Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.

331 Treble Cove Road
Billerica, Massachusetts, USA 01862
For ordering Tel. Toll Free: 800-225-1572
...r other business: 800-362-2668
(For Massachusetts and International, call 508-667-9531)

51-1934

Printed in U.S.A.

February 1991

The Du Pont Merck Pharmaceutical Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862

PYROLITE®

Kit for the preparation of
Technetium Tc99m
Sodium (Pyro- and Trimeta-) Phosphates

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg

Prior to lyophilization the pH is adjusted to between 4.5-5.5 with HCl and/or NaOH. The contents of the vial are lyophilized, stored under nitrogen and contain no bacteriostatic preservative.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic oxidant-free Sodium Pertechnetate Tc99m Injection or isotonic saline.

The precise chemical structure of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates is unknown at this time.

PHYSICAL CHARACTERISTICS

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

Table 1. Principal 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 0.4 microcoulombs/kgMBq-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
0.06	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	Fraction 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: Following intravenous administration of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates, skeletal uptake occurs as a function of blood flow to bone and bone efficiency in extracting the complex. Bone mineral crystals are generally considered to be hydroxyapatite and the complex appears to have an affinity for the hydroxyapatite crystals in bone. It is also concentrated in the injured myocardium, primarily in areas of irreversibly damaged cells.

Clearance of the complex from blood is rapid following intravenous administration. Up to 50% of the injected dose is usually cleared by urinary excretion within the first 3-6 hours. Bone uptake is usually 40-50% within 3 hours following intravenous administration.

INDICATIONS AND USAGE: Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates may be used as a bone imaging agent to delineate areas of altered osteogenesis.

Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates may also be useful in myocardial imaging as an adjunct in the diagnosis of acute myocardial infarction. False negative images can occur if done too early in the evolutionary phase of the infarct or too late in the resolution phase. False positive images have been reported following coronary bypass graft surgery, in unstable angina pectoris, old myocardial infarcts, and in cardiac contusions.

Pyrolite is a blood pool imaging agent which may be used for gated cardiac blood pool imaging and for the detection of sites of gastrointestinal bleeding. When administered intravenously thirty minutes prior to the intravenous administration of Sodium Pertechnetate Tc99m Injection approximately 75% of the injected activity remains in the blood pool.

CONTRAINDICATIONS: None known.

WARNINGS: It has been reported that false-positive or false-negative brain scans may result when brain scans using Sodium Pertechnetate Tc99m are performed after a bone scan has been done using an agent containing stannous chloride, e.g., a pyrophosphate or polyphosphate bone agent. Therefore, in those cases where both brain and bone scans are indicated, the brain scan should be performed first, if feasible. Alternatively, another brain imaging agent, such as Technetium Tc99m DTPA, may be employed.

PRECAUTIONS: If not contraindicated by cardiac status, patients should be encouraged to ingest fluids and to void frequently for the next 4-6 hours in order to minimize radiation dose to the bladder.

The preparation contains no bacteriostatic preservatives.

Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates should be used within six hours of preparation.

The imaging of gastrointestinal bleeding is dependent on such factors as the region of imaging, rate and volume of the bleed, efficacy of labeling of the red blood cells and timeliness of imaging. Due to these factors, images should be taken sequentially over a period of time until a positive image is obtained or clinical conditions warrant the discontinuance of the procedure. The period of time for collecting the images may range up to thirty-six hours.

General

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also care should be taken to minimize radiation exposure to the patients consistent with proper patient management.

The 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 Sodium (Pyro- and Trimeta-) Phosphates affect fertility in males or females.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates. It is also not known whether Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates should be given to a pregnant woman only if clearly needed.

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: Several adverse reactions due to Pyrolite have been reported. These were usually hypersensitivity reactions characterized by itching, various skin rashes, hypotension, fever, chills, nausea, vomiting and dizziness.

DOSAGE AND ADMINISTRATION: The suggested dose range for i.v. administration to be employed in the average patient (70kg) is:

Bone imaging: 185-555MBq (5-15mCi)
Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates
Scanning post-injection is optimal at about 3-4 hours.

Myocardial Imaging: 370-740MBq (10-20mCi)
Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates
Scanning post-injection is optimal at 60-90 minutes.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration. Radiochemical purity should be checked prior to patient administration.

Blood pool imaging: 185-740 MBq (5-20mCi) of sodium pertechnetate Tc99m.

For blood pool imaging the PYROLITE® Kit is reconstituted with three to four ml of sterile Sodium Chloride Injection, U.S.P. and sufficient solution is injected intravenously to yield a patient dose of 14-42mg Sodium (Pyro- and Trimeta-) Phosphates (3-15µg of tin per kilogram body weight). Five to thirty minutes later, 185-740MBq (5 to 20mCi) of Sodium Pertechnetate Tc99m is administered intravenously. Imaging can begin at once for "first pass" studies and after about five minutes for static blood pool imaging.

Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates are prepared by simply adding 3-7ml of sodium pertechnetate Tc99m solution to the vial and swirling for about one minute.

Store at room temperature (15-30°C) before and after reconstitution.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m Sodium (Pyro- and Trimeta-) Phosphates: Preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates complex from the Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates is done by the following aseptic procedure:

Bone and Myocardial Imaging

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the 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 central plastic disk from the vial and swab the top of the vial closure with alcohol to sanitize the surface.

c. Place the reaction vial in a suitable radiation shield with a fitted radiation shield cap.

d. With a sterile, shielded syringe, aseptically obtain 3-7ml (maximum 7.4GBq (200 mCi)) of a suitable, oxidant-free sterile non-pyrogenic Sodium Pertechnetate Tc99m Injection.

e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial.

f. Place the radiation shield cap on the vial shield and swirl the contents of the vial for about one minute to dissolve completely.

g. Maintain adequate shielding during the life of the product by using the radiation vial shield with the radiation shield cap in place and by using a syringe shield for withdrawing and injecting the preparation.

h. Using proper shielding, the vial containing the reconstituted solution should be visually inspected to ensure that it is clear and free of particulate matter and discoloration prior to administration.

i. Assay the product in a suitable dose calibrator, then complete and affix the "radioactive contents" label to the vial shield.

j. Aseptically withdraw material for use within six (6) hours of preparation. Store reconstituted vial at room temperature (15-30°C). The vial contains no preservative.

Do not use if there is a vacuum in the immediate drug container or if air is injected into the container when the dose is withdrawn.

Blood Pool and Gastrointestinal Imaging

a. Reconstitute the reaction vial with three to four milliliters of sterile pyrogen-free isotonic saline without bacteriostat containing no additive agents.

b. Swirl the contents of the vial for about one minute to dissolve completely.

c. The reaction vial should be visually inspected. The resulting solution should be clear and free of particulate matter. If not the reaction vial should not be used.

d. Administer by direct venipuncture. Avoid heparinized catheter systems. Use within six (6) hours of preparation. Store reconstituted vial at room temperature (15-30°C).

RADIATION DOSIMETRY

The effective half-life was assumed to be the physical half-life for all calculated values. About 50% of each dose of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates is retained in the skeleton, and about 50% is excreted into the bladder. The estimated absorbed radiation doses[2] to an average patient (70kg) from an intravenous injection of a maximum dose of 740MBq (20mCi) of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates are shown in Table 4.

VIAL

511935

Tc99m Activity

Time/Date Prepared

See package insert for dosage information.
Reconstitute with 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

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

Contents and Storage Conditions
Sodium Pyrophosphate - 10mg Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
Lyophilized and stored under nitrogen.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

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

DU PONT
PHARMA

Lot No.:
Exp. Date:

C-6A

SHIELD

Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

CAUTION: RADIOACTIVE MATERIAL

Caution: Federal (USA) law prohibits dispensing without prescription.

Contents

Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
Use within 6 hours.

MBq(mCi) Tc99m/ml

Volume ml

Time/Date Prepared

Expiration Time Lot No.

511936

D-7AA

BOX

DU PONT
PHARMA

Pyrolite®
Kit for the preparation of Technetium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS AND STORAGE CONDITIONS:
1 Package Insert, 12 Radiation Labels and 5 Vials, each containing:
Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, Hexahydrate ($SnCl_2 \cdot 2H_2O$) - 0.85mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVES. See Package Insert for Dosage Information.
Reconstitute with sodium Sodium and store at room temperature (15-30°C).
Use within 8 hours.

MARKETED BY
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, MA, U.S.A.

DU PONT
PHARMA

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

CONVENIENCE PACK

DU PONT
PHARMA

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

Contents & Storage Conditions:
1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:
Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

DU PONT
PHARMA

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

STERILE
NON-PYROGENIC
DIAGNOSTIC AGENT FOR
INTRAVENOUS USE.

+ + +

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

+ + +

Tear along perforations
Ready to dispense

Package Insert and Radiation Labels
inside bottom flap.

DU PONT
PHARMA

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517221

DU PONT
PHARMA

Pyrolite®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Marketed by
Du Pont Radiopharmaceutical Division
The Du Pont Merck Pharmaceutical Co.
Billerica, Massachusetts, USA 01862

Open this end for Package Insert and Radiation Labels.

DU PONT
MERCK

Federal Express
7964208052
CUSTOMER PACKAGE TRACKING NUMBER — PULL UP PURPLE TAB

The Du Pont Merck Pharmaceutical Company

March 13, 1991

United States Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, Pa. 19406

Attn.: John D. Kinneman, Chief
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards

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

Gentlemen:

This is a request to amend the above-referenced approval document to reflect a new manufacturer of the reagent kit DTPA and that the FDA has issued an approval for the new drug application recorded as NDA 19-785 for the reagent kit Cardiolite®.

DTPA

The new manufacturer of the reagent kit DTPA will be Merck Frosst Canada, Inc., Kirkland, Quebec, Canada. The previous manufacturer of this material, Cintichem in Tuxedo, NY, will no longer be manufacturing this kit for us after May 1, 1991. There have been no other changes in the formulation of the kit and the product will continue to be distributed by the Du Pont Merck Pharmaceutical operations in Billerica, Massachusetts.

With the exception of the manufacturer change all the other information on the package insert, product labels used on the vials and on the lead shields remain the same as previously submitted to your office. A copy of the revised package insert, labels and packaging markings are enclosed for your information.

Cardiolite®

The information in support of the Cardiolite kit is enclosed as follows:

1. Letter from the Food and Drug Administration, Rockville MD dated December 21, 1990 approving the New Drug Application NDA 19-785.

   Note: The FDA's Notice of Claimed Investigational Exemption for a New Drug IND 28,333 remains valid for this reagent kit.

Radiopharmaceutical Division
331 Treble Cove Road, North Billerica, MA 01862 Telephone 508-667-9531

March 13, 1991

John D. Kinneman
USNRC Region I
475 Allendale Road
King of Prussia, Pa. 19406

2. Revised Package Insert dated 20 December 1990.

3. Vial label, radiation label to be attached to the neck of the vial, and radiation label for the lead shield.

4. Copy of the 2 vial, 5 vial and 30 vial boxes showing package markings.

A check is enclosed in the amount of $250.00 for the amendment processing fee specified for License Fee Category 3D in Title 10 CFR Part 170, Section 170.31.

Please contact me if you require any additional information.

Sincerely,

Francis C Roy Jr.

Francis E. Roy Jr.
Health Physicist

Telephone: (508) 671-8242

2. Remove the protective disc from a reaction vial and swab the rubber septum with an alcohol swab.
3. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 1/8 inch (3 mm) and which has a lifted lead cap. Obtain 2 to 10 mL of sterile, non-pyrogenic sodium pertechnetate Tc 99m using a shielded syringe. The recommended maximum amount of technetium Tc 99m to be added to a reaction vial is 7.4 gigabecquerels (200 mCi). Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.
4. Using a shielded syringe, aseptically add the sodium pertechnetate Tc 99m solution to the reaction vial while avoiding the buildup of excessive pressure in the vial. Pressure buildup may be avoided by injecting several milliliters of pertechnetate solution into the reaction vial, then withdrawing several milliliters of nitrogen gas (present to prevent oxidation of the complex) into the syringe. Repeat the procedure as necessary until the entire amount of the pertechnetate solution is added and normal pressure is established within the vial.
5. Place the lead cap on the vial shield and agitate the shielded vial until the contents are completely dissolved. To ensure maximum tagging, allow the preparation to stand for 15 minutes after mixing. Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.
6. Assay the product in a suitable calibrator, then record the radioassay information on the vial shield label, and affix it to the vial shield.
7. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the reaction vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made from the vial, replacement of the contents with air should be minimized.
8. The finished preparation should be discarded after 6 hours, or if used solely for the estimation of glomerular filtration rate, after 1 hour. It should be retained during its life in a lead vial shield with the lead cap in place.

NOTE: It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent technetium Tc 99m binding), and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded.

This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed to use byproduct material identified in §35.200 of 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and outside the United States, to persons authorized by the appropriate authority.

DUPONT

Marketed by

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
Telephone Toll Free 800-225-1572
(For Mass. & International, Call 617-482-9595)

Manufactured by

Merck Frosst Canada, Inc.
Kirkland, Quebec, Canada

Printed in Canada 27199 0000

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

DTPA

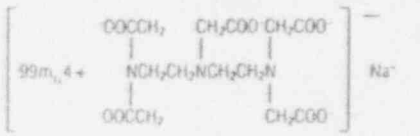
Kit for the Preparation of Technetium Tc 99m Pentetate Injection

DIAGNOSTIC
For Intravenous Use

DESCRIPTION: Each kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Pentetate Injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 25 mg of pentetate calcium trisodium and not less than 0.25 mg stannous chloride dihydrate and not more than 0.385 mg total tin expressed as stannous chloride dihydrate in lyophilized form under an atmosphere of nitrogen. The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH range of the reconstituted radiopharmaceutical is 4 to 5. Addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc 99m solution produces a rapid labeling which is essentially quantitative and which remains stable *in vitro* throughout the 6 hour life of the preparation. No bacteriostatic preservative is present.

The structure of the technetium labeled form is:



Its chemical name is:

Technetate (1-)^{m}-Tc, [*N*-bis[2-[bis(carboxymethyl)amino]ethyl]-glycinato(5-)]-,sodium.

PHYSICAL CHARACTERISTICS

Technetium 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 %/ 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 Technetium 99m is 0.78 R/mCi-hr at 1 cm. The first half value layer is 0.017 cm of lead. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 2.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness lead (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: Tc99m, 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: Following its intravenous administration, technetium Tc 99m pentetate rapidly distributes itself throughout the extracellular fluid space from which it is promptly cleared from the body. The mechanism of excretion from the body is by glomerular filtration. There should be little or no binding of the chelate by the renal parenchyma. A variable percentage of the technetium Tc 99m pentetate binds to the serum proteins, this ranges from 3.7% following a single injection to approximately 10% if the material is continuously infused. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance.

The images of the kidneys obtained in the first few minutes after administration of technetium Tc 99m pentetate represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collection system and the renal pelvis.

Technetium Tc 99m pentetate tends to accumulate in intra-cranial lesions with excessive neovascularity or an altered blood-brain barrier. It does not accumulate in the choroid plexus.

INDICATIONS AND USAGE: Technetium Tc 99m Pentetate Injection may be used to perform kidney imaging, brain imaging; to assess renal perfusion, and to estimate glomerular filtration rate.

CONTRAINDICATIONS: Hypersensitivity to any component of this product.

WARNINGS: None.

PRECAUTIONS:

GENERAL

The contents of the reaction vial before preparation are not radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Pentetate Injection and are not to be administered directly to the patient.

The image quality may be adversely affected by impaired renal function.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to develop fully, and the possibility of missing certain lesions when imaging is restricted to the early period after injection should be borne in mind.

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

Technetium Tc 99m Pentetate Injection should be formulated within six (6) hours prior to clinical use for brain and kidney imaging, and for assessing renal perfusion. For estimating glomerular filtration rates, Technetium Tc 99m Pentetate Injection should be used within one (1) hour after formulation.

The components of the kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the sodium pertechnetate Tc 99m 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 solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m solutions containing oxidants should not be employed.

Technetium Tc 99m Pentetate Injection as well as other radioactive drugs must be handled with care, and appropriate safety measures should be taken to minimize radiation exposure to the patients consistent with proper patient management, and to minimize radiation exposure to clinical personnel.

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.

The preparation contains no bacteriostatic preservative. Therefore, after labeling with technetium Tc 99m, the solution should be stored at 2°C to 8°C in a suitable lead shield.

High background counts, poor images and erroneous clearance results have been observed with the use of vials exceeding the stated expiration time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Pentetate Injection affects fertility in males or females. Mutagenicity studies have not been conducted.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Pentetate Injection. It is also not known whether Technetium Tc 99m Pentetate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Pentetate Injection should be given to a pregnant woman only if clearly needed.

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 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 have not been established.

ADVERSE REACTIONS: Pyrogenic and allergic reactions to technetium Tc 99m pentetate preparations have been reported in the literature.

DOSAGE AND ADMINISTRATION: The recommended dose range for intravenous administration, after reconstitution with oxidant-free sodium pertechnetate Tc 99m, to be administered to the average patient (70 kg) is:

Kidney imaging and glomerular filtration rate estimation	111 to 185 MBq (3 to 5 mCi)
Brain imaging or assessment of renal perfusion	370 to 740 MBq (10 to 20 mCi)

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Store finished preparation at 2°C to 8°C in a suitable lead shield.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution contains particulate matter or is not a clear solution.

RADIATION DOSIMETRY

The estimated absorbed radiation doses[1] to various organs of an average patient (70 kg) from an intravenous injection of maximum doses of 185 MBq (5 mCi) and 740 MBq (20 mCi) of Technetium Tc99m Pentetate Injection are shown in Table 4.

Table 4. Estimated Absorbed Radiation Doses

Organs	Kidney Imaging or GFR estimation		Brain Imaging or Assessment of Renal Perfusion	
	mGy/ 185 MBq	rads/ 5 mCi	mGy/ 740 MBq	rads/ 20 mCi
Kidneys	4.5	0.45	18.0	1.8
Whole Body	0.3	0.03	1.2	0.12
Bladder Wall				
2.0 hr void	5.75	0.58	23.0	2.3
4.8 hr void	13.5	1.35	54.0	5.4
Testes				
2.0 hr void	0.38	0.04	1.5	0.15
4.8 hr void	0.53	0.05	2.1	0.21
Ovaries				
2.0 hr void	0.55	0.06	2.2	0.22
4.8 hr void	0.78	0.08	3.1	0.31

[1]Method of calculation: "S" Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

HOW SUPPLIED: Kit for the Preparation of Technetium Tc 99m Pentetate Injection

Available in cartons containing 5 reaction vials, each reaction vial containing an lyophilized form, sterile and non-pyrogenic:

Pentetate Calcium Trisodium	25 mg
Stannous Chloride Dihydrate (minimum)	0.25 mg
(Maximum tin as stannous chloride dihydrate	0.385 mg)

The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH of the reconstituted radiopharmaceutical is 4 to 5. The vials are sealed under an atmosphere of nitrogen.

Vial shield labels, radiation warning labels, and a package insert are supplied in each carton.

STORAGE: Store the unreconstituted reaction vials at or below room temperature (2°C to 25°C). Store the reconstituted reaction vial at 2°C to 8°C in a suitable lead shield, and discard after 6 hours.

DIRECTIONS FOR PREPARATION

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding. Waterproof gloves should be worn during the preparation procedures.

To prepare Technetium Tc 99m Pentetate Injection:

1. Prior to adding the sodium pertechnetate Tc 99m solution to the vial, write the estimated amount of radioactivity to be added to the vial as well as the date and time of preparation in the spaces provided on the vial label. Then tear off a radiation warning label and attach it to the neck of the vial.

21803 0000

Tc 99m Activity _____

Time/Date Prepared _____

Recommended Adult Dose: 111-740MBq (3-20mCi). See package insert for dosage information. CONTAINS NO BACTERIOSTATIC PRESERVATIVE. FOR INTRAVENOUS USE ONLY AFTER LABELING WITH OXIDANT-FREE TECHNETIUM Tc 99m.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

DUPONT

DTPA

Kit for the Preparation of Technetium Tc 99m Pentetate Injection

CONTENTS & STORAGE CONDITIONS

Pentetate Calcium Trisodium – 25 mg
Stannous Chloride Dihydrate (minimum) – 0.25 mg
(Maximum tin as stannous chloride dihydrate – 0.385 mg)

The pH of the reconstituted drug is 4-5. Sealed under nitrogen. After labeling with Technetium Tc 99m, store solution at 2°C-8°C in a suitable lead shield and use within time limits in package insert.

CAUTION: Federal (USA) law prohibits dispensing without prescription.

Marketed by:
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

Lot No:

Exp. Date:

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m Pentetate Injection

After labeling with oxidant-free Technetium Tc 99m, store solution at 2°C-8°C in a suitable lead shield and use within time h. Its in package insert.

Usual adult dose: 111-740MBq (3-20mCi) of Technetium Tc 99m Pentetate Injection. See package insert for dosage information.

Total Activity MBq (mCi)

Activity Concentration MBq/ml (mCi/ml) | Volume (ml)

Time / Date Prepared

Expiration Time | Lot No

988 0000

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

10369 0000

DU PONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Recommended Adult Dose: 111 to 740 megabecquerels (3 to 20 millicuries). Read enclosed package insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

DU PONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

CONTENTS & STORAGE CONDITIONS: 1 package insert, 6 vial shield labels, 6 radiation warning labels, and 5 reaction vials each containing sterile and non-pyrogenic: Pentetate Calcium Trisodium - 25mg; Stannous Chloride Dihydrate (mikonym) - 0.35mg; (Maximum tin as stannous chloride dihydrate - 0.385mg).
CONTAINS NO BACTERIOSTATIC PRESERVATIVE.
See package insert for dosage information. The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH range of the reconstituted radiopharmaceutical is 4 to 5. Sealed under nitrogen. After labelling with Technetium Tc 99m, store solution at 2°C to 8°C in a suitable lead shield and use within time limits in package insert.

DU PONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

Exp. Date

Lot No:

DU PONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentet

MARKETED BY:
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

MANUFACTURED BY:
Merck Frosst Canada Inc.
Kirkland, Quebec, Canada

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-785

DEC 21 1990

E.I. du Pont de Nemours & Co. (Inc.).
Medical Products Department
331 Treble Cove Road
North Billerica, Massachusetts 01862

Attention: Mary Donovan
Regulatory Affairs Specialist

Dear Ms. Donovan:

Please refer to your new drug application submitted on March 17, 1988 and resubmitted on December 12, 1988 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardiolite (kit for the preparation of technetium Tc 99m sestamibi). We also acknowledge receipt of your presubmission of chemistry information on October 19, 1987 and your amendments and correspondence dated December 21, 1987; April 21 and 22, May 5, 19 and 26, June 10, July 15 and 25, September 30, November 14, December 9 (2), 20 and 22, 1988; January 9, February 9, 17 and 23, March 8, April 4, May 27, June 9, July 5 and 26, October 12, November 6, 8, 15(2), 22, 28 and 30(3), and December 4, 1989; January 17, February 5, 6, 8 and 28, March 6, 10, 16, 22 and 30, April 5, May 2, 16, 29 and 31, June 12 and 26, August 9 and October 9, 23, 30 and 31, November 6, 14, 15, 20 and 27, and December 4 and 20, 1990. We also acknowledge your undated chemistry submission received on March 17, 1988.

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft labeling submitted on December 20, 1990. Accordingly, the application is approved, effective on the date of this letter.

We note your commitment to submit the advertising copy which you intend to use in your proposed promotional and/or advertising campaign and to work with the Agency to resolve any differences as a result of FDA's review of the advertising copy.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed. In such a case, the policy of the Center for Drug Evaluation and Research is to proceed with approval. We note your October 23, 1990 agreement to cooperate in the resolution of any problems that may occur with respect to validation.

The final printed labeling (FPL) must be identical to the draft labeling submitted on December 20, 1990. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as possible. Seven of the copies should be individually mounted on heavy weight paper or similar material. This submission should be designated for administrative purposes as "FPL for approved NDA 19-785". Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of Cardiolite when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PACKAGE INSERT

20 December 1990

USA
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862

CARDIOLITE®

Kit for the preparation of Technetium Tc99m Sestamibi

FOR DIAGNOSTIC USE

DESCRIPTION: Each 5ml vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0mg
Sodium Citrate Dihydrate – 2.6mg
L-Cysteine Hydrochloride Monohydrate – 1.0mg
Mannitol – 20mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) – 0.025mg
Stannous Chloride, Dihydrate, ($SnCl_2 \cdot 2H_2O$) – 0.075mg
Tin Chloride (Stannous and Stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) – 0.086mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0-6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for 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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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, Tc99m Half-Life 6.02 Hours

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

* Calibration Time

CLINICAL PHARMACOLOGY: Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of Thallous Chloride Tl-201. Scintigraphic images obtained in animals and man after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl-201 in normal and abnormal myocardial tissue.

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc99m Sestamibi in plasma. The myocardial biological half-life is approximately six hours after a rest injection. The biological half-life for the liver is approximately 30 minutes after a rest injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 28 minutes, after a rest injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than Thallous Chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose. The following table illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

[Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects.]

Time	Heart		Liver	
	Biological	Effective	Biological	Effective
5 mins	1.2	1.2	20	20
30 mins	1.1	1.0	12	11.3
1 hour	1.0	0.9	5.6	5.0
2 hours	1.0	0.8	2.2	1.7
4 hours	0.8	0.5	0.7	0.4

INDICATIONS AND USAGE: CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium, and in the localization of the abnormality, in patients with suspected myocardial infarction.

CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is also useful in the evaluation of myocardial function using the first pass technique.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after 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

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 rads/30mCi) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability. (See Dosimetry subsection in DOSAGE AND ADMINISTRATION section.)

The active intermediate, $[Cu(MIBI)_4]BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all *in vitro*). At cytotoxic concentrations (≥ 20μg/ml), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. $[Cu(MIBI)_4]BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9mg/kg, > 600 X maximal human dose).

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Sestamibi should be given to a pregnant woman only if clearly needed.

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 Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. 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: During clinical trials, approximately 8% of patients experienced a transient metallic or bitter taste immediately after the injection of Technetium Tc99m Sestamibi. A few cases of transient headache, flushing and non-itching rash have also been attributed to administration of the agent. One patient demonstrated signs and symptoms consistent with seizure 8 to 10 minutes after administration of the drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Sestamibi have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

370-1110MBq (10-30mCi)

The dose administered should be the lowest required to provide an adequate study consistent with ALARA principles (See also PRECAUTIONS).

When used in the diagnosis of myocardial infarction, imaging should be completed within four hours after administration (see also CLINICAL PHARMACOLOGY).

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.

Store at room temperature (15-30°C) before and after reconstitution.

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

Table 4. Radiation Absorbed Doses from Tc99m Sestamibi

	Estimated Radiation Absorbed Dose			
	REST			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30mCi	mGy/ 1110MBq	rads/ 30mCi	mGy/ 1110MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8

Stabin M., July, 1990 Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831 (615) 576-3449

INSTRUCTIONS FOR PREPARATION OF Technetium Tc99m Sestamibi

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

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.
c. Place the vial in a suitable radiation shield with a fitted radiation cap.
d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection [925-5550MBq, (25-150mCi)] in approximately 1 to 3ml.
e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
f. Swirl the contents of the vial for a few seconds.
g. Remove the vial from the lead shield and place upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.
h. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.
i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.
j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.
k. Store the reaction vial containing the Technetium Tc99m Sestamibi at room temperature (15-30°C) until use; at such time the product should be aseptically withdrawn. Technetium Tc99m Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Product should be used within 6 hours after preparation.

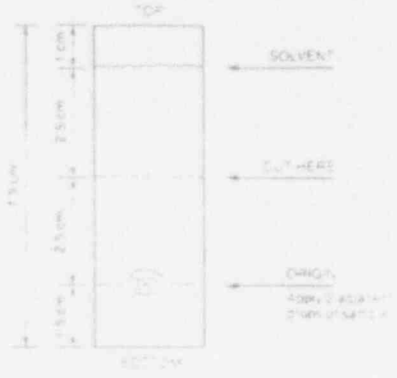
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

DETERMINATION OF RADIOCHEMICAL PURITY IN Technetium Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5cm × 7.5cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1ml syringe with a 22-26 gauge needle, 1.5cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol* to a depth of 3-4mm. Cover the tank and let it equilibrate for ~ 10 minutes.
6. Develop the plate in the covered TLC Tank in ethanol* for a distance of 5cm from the point of application.
7. Cut the TLC plate 4cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc99m Sestamibi as:

$$\%\ Tc99m\ Sestamibi = \frac{\mu Ci\ Top\ Piece}{\mu Ci\ Both\ Pieces} \times 100$$

TLC Plate Diagram



*The ethanol used in this procedure should be [illegible] or greater. [illegible] ethanol (95%) should remain at [illegible] for one week after opening if stored tightly capped [illegible]

HOW SUPPLIED: Du Pont's CARDIOLITE® , Kit for the preparation of Technetium Tc99m Sestamibi is supplied as a 5ml vial in kits of two (2), five (5) and thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vials are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each two (2) vial kit is one (1) package insert, five (5) vial shield labels and five (5) radiation warning labels. Included in each five (5) vial kit is one (1) package insert, five (5) vial shield labels and five (5) radiation warning labels. Included in each thirty (30) vial kit is one (1) package insert, thirty (30) vial shield labels and thirty (30) radiation warning labels.

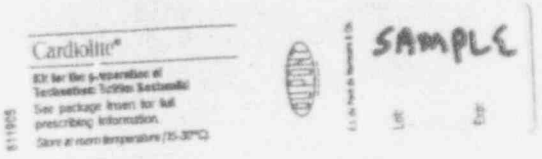
The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in 35.100 and 35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

DUPONT

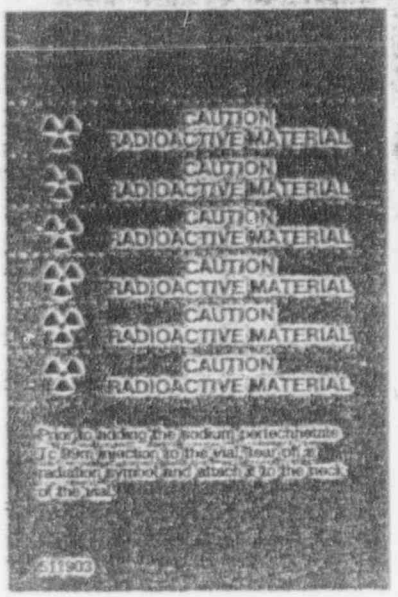
Marketed by
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 617-482-9595)

Printed in U.S.A.

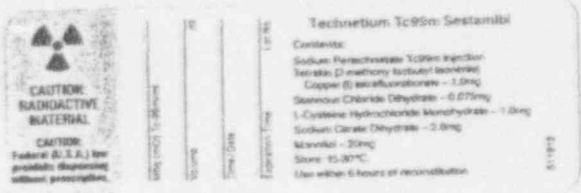
VIAL LABEL


Cardiolite®
Kit for the preparation of
Technetium Tc99m Sestamibi
See package insert for full
prescribing information.
Store at room temperature (15-30°C)
611905
SAMPLE

RADIATION LABEL (VIAL)



RADIATION LABEL (LEAD SHIELD)



2 VIAL BOX

DUPONT

Cardiolite®

KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

DUPONT

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

DUPONT

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E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

517204

DUPONT

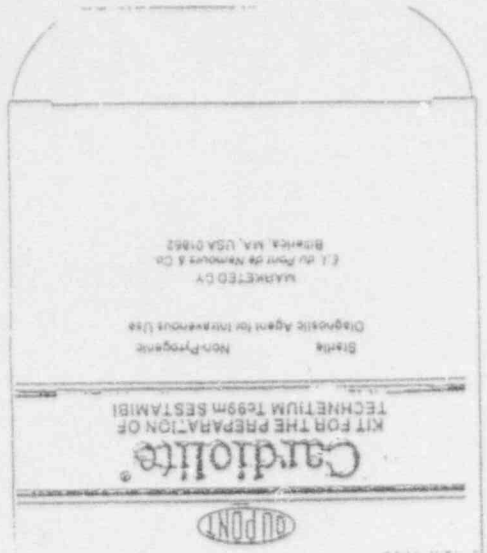
Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI

Sterile Non-Pyrogenic
Diagnostic Agent for Intravenous Use

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

Contents & Storage Conditions:
1 Package Insert, 10 Radiation labels & 2 Vials each containing:
Tetrakis (2-methoxy Isobutyl Isonitrile) Copper (I) tetrafluoroborate – 1.0mg
Stannous Chloride Dihydrate – 0.075mg
L-Cysteine Hydrochloride Monohydrate – 1.0mg
Sodium Citrate Dihydrate – 2.6mg
Mannitol – 20mg
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVES
See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours of reconstitution.

5 VIAL BOX



CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Contents & Storage Conditions:
1 Package Insert, 10 Radiation labels & 5 Vials each containing:
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0mg
Stannous Chloride Dihydrate – 0.075mg
L-Cysteine Hydrochloride Monohydrate – 1.0mg
Sodium Citrate Dihydrate – 2.8mg
Mannitol – 20mg
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVES
See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 8 hours of reconstitution.

DUPONT

Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI

DUPONT

MARKETED BY
E. I. du Pont de Nemours & Co.
Billerica, MA. USA 01862

0 VIAL BOX

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

Cardiolite®

KIT FOR THE PREPARATION OF TECHNETIUM Tc99m SESTAMIBI

Contents & Storage Conditions:
1 Package Insert, 60 Radiation labels & 30 Vials each containing:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate - 1.0mg

Stannous Chloride Dihydrate - 0.075mg

L-Cysteine Hydrochloride Monohydrate - 1.0mg

Sodium Citrate Dihydrate - 2.6mg

Mannitol - 29mg

Store at room temperature (15-30°C)

CONTAINS NO PRESERVATIVES

See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours of reconstitution.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use.

CONVENIENT RE-ORDER POINT (maximum fifteen vials)

(maximum six vials)

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Tear along perforations
Ready to dispense

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

517209

Carton Ends for Package Insert and Radiation Labels

DUPONT

E.I. DU PONT DE NEMOURS & COMPANY

05405115

0-000-002343820 DUPONT ACCOUNTS PAYABLE 05405115 02/08/91

INVOICE NO.	P.O. NUMBER	DATE	GROSS	DISCOUNT %	NET
020191	YDM11223702-01-91		250.00	.00	250.00
LEASE: 000027335					
TOTALS			250.00	.00	250.00

[redacted]

DUPONT

E I du Pont de Nemours & Company

INCORPORATED

05405115

64-1327/611

FIN 01 FINANCE DEPT. - DISBURSEMENTS WILMINGTON, DELAWARE 19898

DATE 02/08/91

CHECK NUMBER 05405115

AMOUNT $*********250.00

PAY TO THE ORDER OF

US GOVT
OFFICE OF THE CONTROLLER
US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

NOT VALID AFTER 90 DAYS

M. T. Sharples

FIRSTATLANTA
The First National Bank of Atlanta
Augusta, Georgia

DUPONT

Better Things for Better Living . . . from Du Pont

⑈05405115⑈ ⑆061113279⑆ 07 519 318⑈

DU PONT
MERCK

The Du Pont Merck Pharmaceutical Company

March 13, 1991

United States Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, Pa. 19406

Attn.: John D. Kinneman, Chief
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards

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

Gentlemen:

This is a request to amend the above-referenced approval document to reflect a new manufacturer of the reagent kit DTPA and that the FDA has issued an approval for the new drug application recorded as NDA 19-785 for the reagent kit Cardiolite®.

DTPA

The new manufacturer of the reagent kit DTPA will be Merck Frosst Canada, Inc., Kirkland, Quebec, Canada. The previous manufacturer of this material, Cintichem in Tuxedo, NY, will no longer be manufacturing this kit for us after May 1, 1991. There have been no other changes in the formulation of the kit and the product will continue to be distributed by the Du Pont Merck Pharmaceutical operations in Billerica, Massachusetts.

With the exception of the manufacturer change all the other information on the package insert, product labels used on the vials and on the lead shields remain the same as previously submitted to your office. A copy of the revised package insert, labels and packaging markings are enclosed for your information.

Cardiolite®

The information in support of the Cardiolite kit is enclosed as follows:

1. Letter from the Food and Drug Administration, Rockville MD dated December 21, 1990 approving the New Drug Application NDA 19-785.

   Note: The FDA's Notice of Claimed Investigational Exemption for a New Drug IND 28,333 remains valid for this reagent kit.

Radiopharmaceutical Division
331 Treble Cove Road, North Billerica, MA 01862 Telephone 508-667-9531

March 13, 1991

John D. Kinneman
USNRC Region I
475 Allendale Road
King of Prussia, Pa. 19406

2. Revised Package Insert dated 20 December 1990.

3. Vial label, radiation label to be attached to the neck of the vial, and radiation label for the lead shield.

4. Copy of the 2 vial, 5 vial and 30 vial boxes showing package markings.

A check is enclosed in the amount of $250.00 for the amendment processing fee specified for License Fee Category 3D in 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

Telephone: (508) 671-8242

2. Remove the protective disc from a reaction vial and swab the rubber septum with an alcohol swab.

3. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 1/8 inch (3 mm) and which has a fitted lead cap. Obtain 2 to 10 mL of sterile, non-pyrogenic sodium pertechnetate Tc 99m using a shielded syringe. The recommended maximum amount of technetium Tc 99m to be added to a reaction vial is 7.4 gigabecquerels (200 mCi). Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.

4. Using a shielded syringe, aseptically add the sodium pertechnetate Tc 99m solution to the reaction vial while avoiding the buildup of excessive pressure in the vial. Pressure buildup may be avoided by injecting several milliliters of pertechnetate solution into the reaction vial, then withdrawing several milliliters of nitrogen gas (present to prevent oxidation of the complex) into the syringe. Repeat the procedure as necessary until the entire amount of the pertechnetate solution is added and normal pressure is established within the vial.

5. Place the lead cap on the vial shield and agitate the shielded vial until the contents are completely dissolved. To ensure maximum tagging, allow the preparation to stand for 15 minutes after mixing. Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.

6. Assay the product in a suitable calibrator, then record the radioassay information on the vial shield label, and affix it to the vial shield.

7. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the reaction vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made from the vial, replacement of the contents with air should be minimized.

8. The finished preparation should be discarded after 6 hours, or if used solely for the estimation of glomerular filtration rate, after 1 hour. It should be retained during its life in a lead vial shield with the lead cap in place.

NOTE: It is recommended that with proper shielding and equipment, the final formulation be tested for radiochemical purity (percent technetium Tc 99m binding), and each patient dose be visually inspected for foreign matter. If the radiochemical purity is not adequate or foreign matter is observed in the patient dose, it is recommended that the patient dose be discarded.

This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed to use byproduct material identified in §35.200 of 10 CFR Part 35, to persons who have a similar authorization issued by an Agreement State, and outside the United States, to persons authorized by the appropriate authority.

DU PONT

Marketed by

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862
Telephone Toll Free 800 225 1572
(For Mass. & International, Call 617-482-9595)

Manufactured by

Merck Frosst Canada, Inc.
Kirkland, Quebec, Canada

Printed in Canada 27199 0000

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

DTPA

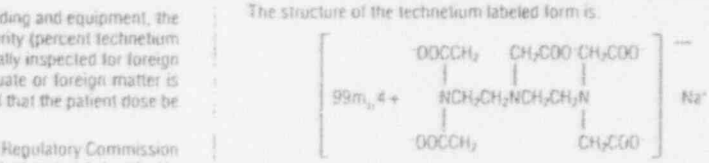
Kit for the Preparation of Technetium Tc 99m Pentetate Injection

DIAGNOSTIC
For Intravenous Use

DESCRIPTION: Each kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Pentetate Injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 25 mg of pentetate calcium trisodium and not less than 0.25 mg stannous chloride dihydrate and not more than 0.385 mg total tin expressed as stannous chloride dihydrate in lyophilized form under an atmosphere of nitrogen. The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH range of the reconstituted radiopharmaceutical is 4 to 5. Addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc 99m solution produces a rapid labeling which is essentially quantitative and which remains stable *in vitro* throughout the 6 hour life of the preparation. No bacteriostatic preservative is present.

The structure of the technetium labeled form is:



Its chemical name is:

Technetate (1-)^{99m}-Tc, [*N*,*N*-bis[2-[bis(carboxymethyl)amino]ethyl]-glycinato(5-)]-, sodium.

PHYSICAL CHARACTERISTICS

Technetium 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 % 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 Technetium 99m is 0.78 R/mCi-hr at 1 cm. The first half-value layer is 0.017 cm of lead. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 0.25 cm thickness of lead will attenuate the radiation emitted by a factor of about 1,000. A range of values for the relative attenuation of the radiation resulting from the interposition of various thicknesses of lead is shown in Table 2.

Table 2. Radiation Attenuation by Lead Shielding

Shield Thickness lead (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: Tc99m, 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: Following its intravenous administration, technetium Tc 99m pentetate rapidly distributes itself throughout the extracellular fluid space from which it is promptly cleared from the body. The mechanism of excretion from the body is by glomerular filtration. There should be little or no binding of the chelate by the renal parenchyma. A variable percentage of the technetium Tc 99m pentetate binds to the serum proteins; this ranges from 3.7% following a single injection to approximately 10% if the material is continuously infused. Although the chelate gives useful information on the glomerular filtration rate, the variable percent which is protein bound leads to a measured clearance rate which is lower than that determined by inulin clearance.

The images of the kidneys obtained in the first few minutes after administration of technetium Tc 99m pentetate represent the vascular pool within the kidney. Subsequent images of the kidneys represent radioactivity which is in the urine of both the collection system and the renal pelvis.

Technetium Tc 99m pentetate tends to accumulate in intra-cranial lesions with excessive neovascularity or an altered blood-brain barrier. It does not accumulate in the choroid plexus.

INDICATIONS AND USAGE: Technetium Tc 99m Pentetate Injection may be used to perform kidney imaging, brain imaging, to assess renal perfusion, and to estimate glomerular filtration rate.

CONTRAINDICATIONS: Hypersensitivity to any component of this product.

WARNINGS: None.

PRECAUTIONS:

GENERAL

The contents of the reaction vial before preparation are non-radioactive. However, after the sodium pertechnetate Tc 99m is added, adequate shielding of the final preparation must be maintained.

Contents of the reaction vial are intended only for use in the preparation of Technetium Tc 99m Pentetate Injection and are not to be administered directly to the patient.

The image quality may be adversely affected by impaired renal function.

Literature reports indicate that the target to non-target ratio for intracranial lesions may take several hours to develop fully, and the possibility of missing certain lesions when imaging is restricted to the early period after injection should be borne in mind.

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

Technetium Tc 99m Pentetate Injection should be formulated within six (6) hours prior to clinical use for brain and kidney imaging, and for assessing renal perfusion. For estimating glomerular filtration rates, Technetium Tc 99m Pentetate Injection should be used within one (1) hour after formulation.

The components of the kit are supplied sterile and non-pyrogenic. Aseptic procedures normally employed in making additions and withdrawals from sterile, non-pyrogenic containers should be used during the addition of the sodium pertechnetate Tc 99m 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 solution may thus adversely affect the quality of the radiopharmaceutical. Hence, sodium pertechnetate Tc 99m solutions containing oxidants should not be employed.

Technetium Tc 99m Pentetate Injection as well as other radioactive drugs must be handled with care, and appropriate safety measures should be taken to minimize radiation exposure to the patients consistent with proper patient management, and to minimize radiation exposure to clinical personnel.

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.

The preparation contains no bacteriostatic preservative. Therefore, after labeling with technetium Tc 99m, the solution should be stored at 2°C to 8°C in a suitable lead shield.

High background counts, poor images and erroneous clearance results have been observed with the use of vials exceeding the stated expiration time.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential or whether Technetium Tc 99m Pentetate Injection affects fertility in males or females. Mutagenicity studies have not been conducted.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Pentetate Injection. It is also not known whether Technetium Tc 99m Pentetate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc 99m Pentetate Injection should be given to a pregnant woman only if clearly needed.

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 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 have not been established.

ADVERSE REACTIONS: Pyrogenic and allergic reactions to technetium Tc 99m pentetate preparations have been reported in the literature.

DOSAGE AND ADMINISTRATION: The recommended dose range for intravenous administration, after reconstitution with oxidant-free sodium pertechnetate Tc 99m, to be administered to the average patient (70 kg) is:

Kidney imaging and glomerular filtration rate estimation	111 to 185 MBq (3 to 5 mCi)
Brain imaging or assessment of renal perfusion	370 to 740 MBq (10 to 20 mCi)

To minimize the radiation dose to the bladder, the patient should be encouraged to increase his fluid intake, and to void when the examination is completed and as often thereafter as possible for the next 4 to 6 hours.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Store finished preparation at 2°C to 8°C in a suitable lead shield.

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if the solution contains particulate matter or is not a clear solution.

* **RADIATION DOSIMETRY**

The estimated absorbed radiation doses[2] to various organs of an average patient (70 kg) from an intravenous injection of maximum doses of 185 MBq (5 mCi) and 740 MBq (20 mCi) of Technetium Tc99m Pentetate Injection are shown in Table 4.

Table 4. Estimated Absorbed Radiation Doses

Organs	Kidney Imaging or GFR estimation		Brain Imaging or Assessment of Renal Perfusion	
	mGy/ 185 MBq	rads/ 5 mCi	mGy/ 740 MBq	rads/ 20 mCi
Kidneys	4.5	0.45	18.0	1.8
Whole Body	0.3	0.03	1.2	0.12
Bladder Wall				
2.0 hr void	5.75	0.58	23.0	2.3
4.8 hr void	13.5	1.35	54.0	5.4
Testes				
2.0 hr void	0.38	0.04	1.5	0.15
4.8 hr void	0.53	0.05	2.1	0.21
Ovaries				
2.0 hr void	0.55	0.06	2.2	0.22
4.8 hr void	0.78	0.08	3.1	0.31

[2]Method of calculation: "S" Absorbed Dose per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

HOW SUPPLIED: Kit for the Preparation of Technetium Tc 99m Pentetate Injection

Available in cartons containing 5 reaction vials, each reaction vial containing an lyophilized form, sterile and non-pyrogenic:

Pentetate Calcium Trisodium	25 mg
Stannous Chloride Dihydrate (minimum)	0.25 mg
(Maximum tin as stannous chloride dihydrate	0.385 mg)

The pH is adjusted with HCl or NaOH prior to lyophilization so that the pH of the reconstituted radiopharmaceutical is 4 to 5. The vials are sealed under an atmosphere of nitrogen.

Vial shield labels, radiation warning labels, and a package insert are supplied in each carton.

STORAGE: Store the unreconstituted reaction vials at or below room temperature (7°C to 25°C). Store the reconstituted reaction vial at 2°C to 8°C in a suitable lead shield, and discard after 6 hours.

DIRECTIONS FOR PREPARATION

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure by use of suitable shielding. Waterproof gloves should be worn during the preparation procedures.

To prepare Technetium Tc 99m Pentetate Injection:

1. Prior to adding the sodium pertechnetate Tc 99m solution to the vial, write the estimated amount of radioactivity to be added to the vial as well as the date and time of preparation in the spaces provided on the vial label. Then tear off a radiation warning label and attach it to the neck of the vial.

21803 0000
Tc 99m Activity _____
Time/Date Prepared _____
Recommended Adult Dose: 111-740MBq (3-20mCi). See package insert for dosage information. CONTAINS NO BACTERIOSTATIC PRESERVATIVE. FOR INTRAVENOUS USE ONLY AFTER LABELING WITH OXIDANT-FREE TECHNETIUM Tc 99m.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

DUPONT

DTPA

Kit for the Preparation of Technetium Tc 99m Pentetate Injection

CONTENTS & STORAGE CONDITIONS
Pentetate Calcium Trisodium – 25 mg
Stannous Chloride Dihydrate (minimum) – 0.25 mg
(Maximum tin as stannous chloride dihydrate – 0.385 mg)
The pH of the reconstituted drug is 4-5. Sealed under nitrogen. After labeling with Technetium Tc 99m, store solution at 2°C-8°C in a suitable lead shield and use within time limits in package insert.
CAUTION: Federal (USA) law prohibits dispensing without prescription.
Marketed by:
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

Lot No:
Exp. Date:

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription

Technetium Tc 99m Pentetate Injection

After labeling with oxidant-free Technetium Tc 99m, store solution at 2°C-8°C in a suitable lead shield and use within time limits in package insert.

Usual adult dose: 111-740MBq (3-20mCi) of Technetium Tc 99m Pentetate Injection. See package insert for dosage information.

Total Activity MBq (mCi)

Activity Concentration MBq/mL (mCi/mL) Volume (mL)

Time / Date Prepared

Expiration Time Lot No.

986 0000

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

10369 0000

Pentetate Injection

e insert, 6 vial shield
als each containing
tium – 25mg; Stannous
n tin as stannous

E
is adjusted with HCl
of the reconstituted
n. After labeling with
a suitable lead shield

DUPONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

Exp. Date:

Lot No:

DUPONT

DTPA

Kit for the preparation of Technetium Tc 99m Pentetate Injection

MARKETED BY:
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

MANUFACTURED BY:
Merck Frosst Canada Inc.
Kirkland, Quebec, Canada

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-785

DEC 21 1990

E.I. du Pont de Nemours & Co. (Inc.).
Medical Products Department
331 Treble Cove Road
North Billerica, Massachusetts 01862

Attention: Mary Donovan
Regulatory Affairs Specialist

Dear Ms. Donovan:

Please refer to your new drug application submitted on March 17, 1988 and resubmitted on December 12, 1988 under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Cardiolite (kit for the preparation of technetium Tc 99m sestamibi). We also acknowledge receipt of your resubmission of chemistry information on October 19, 1987 and your amendments and correspondence dated December 21, 1987; April 2[illegible] 4, May 5, 19 and 26, June 10, July 15 and 25, September 30, November 14, December 9 (2), 20 and 22, 1988; January 9, February 9, 17 and 23, March 8, April 4, May 27, June 9, July 5 and 26, October 12, November 6, 8, 15(2), 22, 28 and 30(3), and December 4, 1989; January 17, February 5, 6, 8 and 28, March 6, 10, 16, 22 and 30, April 5, May 2, 16, 29 and 31, June 12 and 26, August 9 and October 9, 23, 30 and 31, November 6, 14, 15, 20 and 27, and December 4 and 20, 1990. We also acknowledge your undated chemistry submission received on March 17, 1988.

We have completed the review of this application as amended, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the draft labeling submitted on December 20, 1990. Accordingly, the application is approved, effective on the date of this letter.

We note your commitment to submit the advertising copy which you intend to use in your proposed promotional and/or advertising campaign and to work with the Agency to resolve any differences as a result of FDA's review of the advertising copy.

While all other aspects of this application have been found to be approvable, the required validation of the analytical methods has not been completed. In such a case, the policy of the Center for Drug Evaluation and Research is to proceed with approval. We note your October 23, 1990 agreement to cooperate in the resolution of any problems that may occur with respect to validation.

The final printed labeling (FPL) must be identical to the draft labeling submitted on December 20, 1990. Marketing the product with FPL that is not identical to the draft labeling may render the product misbranded and an unapproved new drug. Please submit twelve copies of the FPL to FDA as soon as possible. Seven of the copies should be individually mounted on heavy weight paper or similar material. This submission should be designated for administrative purposes as "FPL for approved NDA 19-785". Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of this drug product become available prior to our receipt of the final printed labeling, revision of that labeling may be required.

Please submit one market package of Cardiolite when available.

We remind you that you must comply with the requirements set forth under 21 CFR 314.80 and 314.81 for an approved NDA.

Sincerely yours,

Paula Botstein MD

Paula Botstein, M.D.
Deputy Director (Medical Affairs)
Office of Drug Evaluation I
Center for Drug Evaluation and Research

PACKAGE INSERT

20 December 1990

USA
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862

CARDIOLITE®

Kit for the preparation of Technetium Tc99m Sestamibi

FOR DIAGNOSTIC USE

DESCRIPTION: Each 5ml vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0mg
Sodium Citrate Dihydrate – 2.6mg
L-Cysteine Hydrochloride Monohydrate – 1.0mg
Mannitol – 20mg
Stannous Chloride, Dihydrate, minimum ($SnCl_2 \cdot 2H_2O$) – 0.025mg
Stannous Chloride, Dihydrate, ($SnCl_2 \cdot 2H_2O$) – 0.075mg
Tin Chloride (Stannous and Stannic) Dihydrate, maximum (as $SnCl_2 \cdot 2H_2O$) – 0.086mg

Prior to lyophilization the pH is 5.3 to 5.9. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m Injection. The pH of the reconstituted product is 5.5 (5.0-6.0). No bacteriostatic preservative is present.

The precise structure of the technetium complex is $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxy isobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours.[1] Photons that are useful for 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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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, Tc99m Half-Life 6.02 Hours

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

* Calibration Time

CLINICAL PHARMACOLOGY: Tc99m Sestamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in a manner analogous to that of Thallous Chloride Tl-201. Scintigraphic images obtained in animals and man after the intravenous administration of the drug have been comparable to those obtained with Thallous Chloride Tl-201 in normal and abnormal myocardial tissue.

The major pathway for clearance of Tc99m Sestamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty-seven percent of the injected dose is excreted in the urine, and approximately thirty-three percent of the injected dose is cleared through the feces in 48 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that the fast clearing component clears with a $t_{1/2}$ of 4.3 minutes at rest. At five minutes post injection about 8% of the injected dose remains in circulation. There is less than 1% protein binding of Technetium Tc99m Sestamibi in plasma. The myocardial biological half-life is approximately six hours after a rest injection. The biological half-life for the liver is approximately 30 minutes after a rest injection. The effective half-life of clearance (which includes both the biological half-life and radionuclide decay) for the heart is approximately 3 hours, and for the liver is approximately 28 minutes, after a rest injection. The ideal imaging time reflects the best compromise between heart count rate and surrounding organ uptake.

A study in a dog myocardial ischemia model reported that Technetium Tc99m Sestamibi undergoes myocardial distribution (redistribution), although more slowly and less completely than Thallous Chloride Tl-201. A study in a dog myocardial infarction model reported that the drug showed no redistribution of any consequence. Definitive human studies to demonstrate possible redistribution have not been reported. In patients with documented myocardial infarction, imaging revealed the infarct up to four hours post dose.

Animal studies have shown that myocardial uptake is not blocked when the sodium pump mechanism is inhibited. Myocardial uptake which is coronary flow dependent is 1.2% of the injected dose. The following table illustrates the biological clearance as well as effective clearance (which includes biological clearance and radionuclide decay) of Tc99m Sestamibi from the heart and liver.

[Organ concentrations expressed as percentage of injected dose; data based on an average of 5 subjects.]

Time	Heart		Liver	
	Biological	Effective	Biological	Effective
5 mins	1.2	1.2	20	20
30 mins	1.1	1.0	12	11.3
1 hour	1.0	0.9	5.6	5.0
2 hours	1.0	0.8	2.2	1.7
4 hours	0.8	0.5	0.7	0.4

INDICATIONS AND USAGE: CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is a myocardial perfusion agent that is useful in distinguishing normal from abnormal myocardium, and in the localization of the abnormality, in patients with suspected myocardial infarction.

CARDIOLITE®, Kit for the preparation of Technetium Tc99m Sestamibi is also useful in the evaluation of myocardial function using the first pass technique.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure.

PRECAUTIONS:

GENERAL

The contents of the vial are intended only for use in the preparation of Technetium Tc99m Sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel. Also, care should be taken 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.

Technetium Tc99m labeling reactions involved depend on maintaining the stannous ion in the reduced state. Hence, Sodium Pertechnetate Tc99m Injection containing oxidants should not be used.

Technetium Tc99m Sestamibi should not be used more than six hours after 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

In comparison with most other diagnostic technetium labeled radiopharmaceuticals, the radiation dose to the ovaries (1.5 rads/30mCi) is high. Minimal exposure (ALARA) is necessary in women of childbearing capability. (See Dosimetry subsection in DOSAGE AND ADMINISTRATION section.)

The active intermediate, $[Cu(MIBI)_4]BF_4$, was evaluated for genotoxic potential in a battery of five tests. No genotoxic activity was observed in the Ames, CHO/HPRT and sister chromatid exchange tests (all *in vitro*). At cytotoxic concentrations ($\geq 20\mu g/ml$), an increase in cells with chromosome aberrations was observed in the *in vitro* human lymphocyte assay. $[Cu(MIBI)_4]BF_4$ did not show genotoxic effects in the *in vivo* mouse micronucleus test at a dose which caused systemic and bone marrow toxicity (9mg/kg, > 600 X maximal human dose).

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m Sestamibi. It is also not known whether Technetium Tc99m Sestamibi can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. There have been no studies in pregnant women. Technetium Tc99m Sestamibi should be given to a pregnant woman only if clearly needed.

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 Pertechnetate is excreted in human milk during lactation. It is not known whether Technetium Tc99m Sestamibi is excreted in human milk. 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: During clinical trials, approximately 8% of patients experienced a transient metallic or bitter taste immediately after the injection of Technetium Tc99m Sestamibi. A few cases of transient headache, flushing and non-itching rash have also been attributed to administration of the agent. One patient demonstrated signs and symptoms consistent with seizure 8 to 10 minutes after administration of the drug. No other adverse reactions specifically attributable to the use of Technetium Tc99m Sestamibi have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for I.V. administration to be employed in the average patient (70kg) is:

370-1110MBq (10-30mCi)

The dose administered should be the lowest required to provide an adequate study consistent with ALARA principles (See also PRECAUTIONS).

When used in the diagnosis of myocardial infarction, imaging should be completed within four hours after administration (see also CLINICAL PHARMACOLOGY).

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.

Store at room temperature (15-30°C) before and after reconstitution.

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

Table 4. Radiation Absorbed Doses from Tc99m Sestamibi

	Estimated Radiation Absorbed Dose			
	REST			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30mCi	mGy/ 1110MBq	rads/ 30mCi	mGy/ 1110MBq
Breasts	0.2	2.0	0.2	1.9
Gallbladder Wall	2.0	20.0	2.0	20.0
Small Intestine	3.0	30.0	3.0	30.0
Upper Large Intestine Wall	5.4	55.5	5.4	55.5
Lower Large Intestine Wall	3.9	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	5.8
Heart Wall	0.5	5.1	0.5	4.9
Kidneys	2.0	20.0	2.0	20.0
Liver	0.6	5.8	0.6	5.7
Lungs	0.3	2.8	0.3	2.7
Bone Surfaces	0.7	6.8	0.7	6.4
Thyroid	0.7	7.0	0.7	6.8
Ovaries	1.5	15.5	1.6	15.5
Testes	0.3	3.4	0.4	3.9
Red Marrow	0.5	5.1	0.5	5.0
Urinary Bladder Wall	2.0	20.0	4.2	41.1
Total Body	0.5	4.8	0.5	4.8

Stabin M., July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831, (615) 576-3449.

INSTRUCTIONS FOR PREPARATION OF Technetium Tc99m Sestamibi
Preparation of the Technetium Tc99m Sestamibi from the Kit for the preparation of Technetium Tc99m Sestamibi is done by the following aseptic procedure:

a. Prior to adding the Sodium Pertechnetate Tc99m Injection to the vial, 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 the vial and swab the top of the vial closure with alcohol to sanitize the surface.
c. Place the vial in a suitable radiation shield with a fitted radiation cap.
d. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection [925-5550MBq, (25-150mCi)] in approximately 1 to 3ml.
e. Aseptically add the Sodium Pertechnetate Tc99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
f. Swirl the contents of the vial for a few seconds.
g. Remove the vial from the lead shield and place upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.
h. Remove the vial from the water bath, place in the lead shield and allow to cool for fifteen minutes.
i. Using proper shielding, the vial contents should be visually inspected. Use only if the solution is clear and free of particulate matter and discoloration.
j. Assay the reaction vial using a suitable radioactivity calibration system. Record the Technetium Tc99m concentration, total volume, assay time and date, expiration time and lot number on the vial shield label and affix the label to the shield.
k. Store the reaction vial containing the Technetium Tc99m Sestamibi at room temperature (15-30°C) until use; at such time the product should be aseptically withdrawn. Technetium Tc99m Sestamibi should be used within six hours of preparation. The vial contains no preservative.

Note: Adherence to the above product reconstitution instructions is recommended.

Product should be used within 6 hours after preparation.

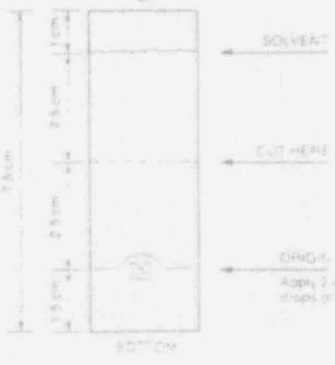
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method:

DETERMINATION OF RADIOCHEMICAL PURITY IN Technetium Tc99m Sestamibi

1. Obtain a Baker-Flex Aluminum Oxide coated, plastic TLC plate, #1 B-F, pre-cut to 2.5cm x 7.5cm.
2. Dry the plate or plates at 100°C for 1 hour and store in a desiccator. Remove pre-dried plate from the desiccator just prior to use.
3. Apply 1 drop of ethanol* using a 1ml syringe with a 22-26 gauge needle, 1.5cm from the bottom of the plate. THE SPOT SHOULD NOT BE ALLOWED TO DRY.
4. Add 2 drops of Technetium Tc99m Sestamibi solution, side by side on top of the ethanol* spot. Return the plate to a desiccator and allow the sample spot to dry (typically 15 minutes).
5. The TLC tank is prepared by pouring ethanol* to a depth of 3-4mm. Cover the tank and let it equilibrate for ~ 10 minutes.
6. Develop the plate in the covered TLC Tank in ethanol* for a distance of 5cm from the point of application.
7. Cut the TLC plate 4cm from the bottom and measure the Tc99m activity in each piece by appropriate radiation detector.
8. Calculate the % Tc99m Sestamibi as:

$$\%\ \text{Tc99m Sestamibi} = \frac{\mu\text{Ci Top Piece}}{\mu\text{Ci Both Pieces}} \times 100$$

TLC Plate Diagram



*The ethanol used in this procedure should be 95% or greater. Absolute ethanol (99+%) should remain at ≥99% ethanol concentration one week after opening if stored tightly capped at room temperature.

HOW SUPPLIED: Du Pont's CARDIOLITE® Kit for the preparation of Technetium Tc99m Sestamibi is supplied as a 5ml vial in kits of two (2), five (5) and thirty (30) vials, sterile and non-pyrogenic.

Prior to lyophilization the pH is between 5.3-5.9. The contents of the vials are lyophilized and stored under nitrogen. Store at room temperature (15-30°C) before and after reconstitution. Technetium Tc99m Sestamibi contains no preservatives. Included in each two (2) vial kit is one (1) package insert, five (5) vial shield labels and five (5) radiation warning labels. Included in each five (5) vial kit is one (1) package insert, five (5) vial shield labels and five (5) radiation warning labels. Included in each thirty (30) vial kit is one (1) package insert, thirty (30) vial shield labels and thirty (30) radiation warning labels.

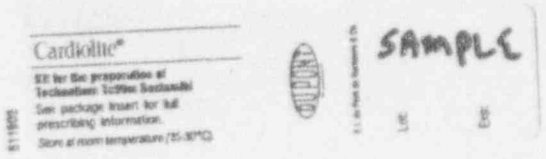
The U.S. Nuclear Regulatory Commission has approved this reagent kit for distribution to persons licensed to use byproduct material identified in 35.100 and 35.200 of 10 CFR Part 35, to persons who hold an equivalent license issued by an Agreement State, and, outside the United States, to persons authorized by the appropriate authority.

DUPONT

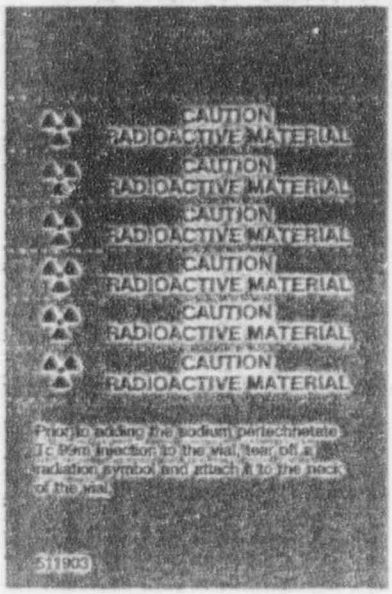
Marketed by
E. I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 617-482-9595)

Printed in U.S.A.

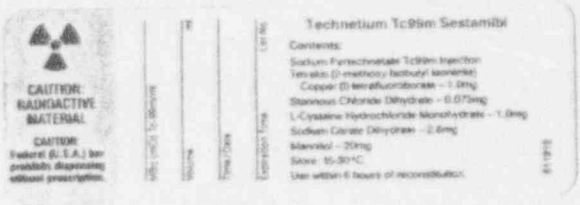
VIAL LABEL


Cardiolite®
Kit for the preparation of
Technetium Tc99m Sestamibi
See package insert for full
prescribing information.
Store at room temperature (15-30°C).
SAMPLE

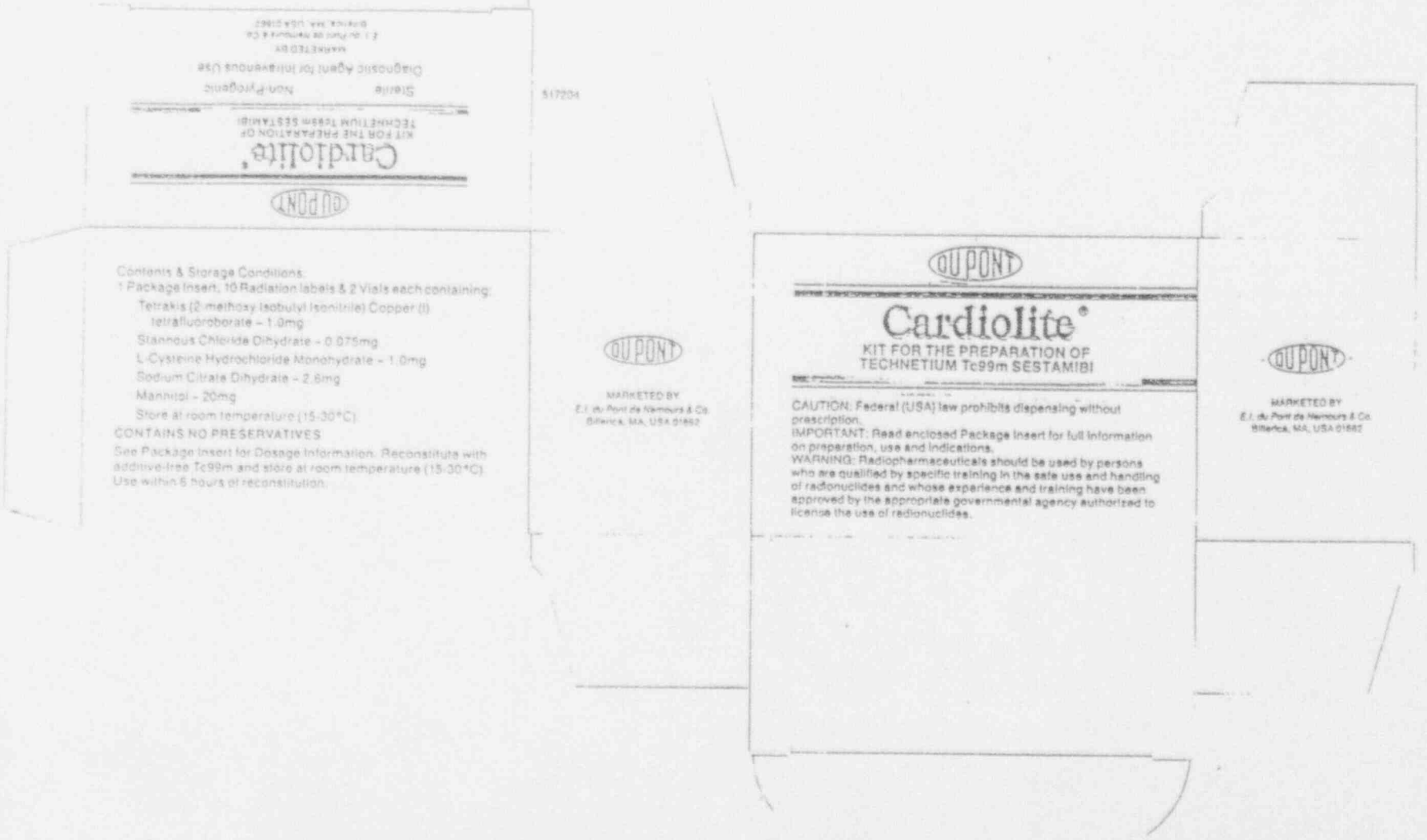
RADIATION LABEL (VIAL)



RADIATION LABEL (LEAD SHIELD)



2 VIAL BOX


DUPONT
Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI
CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862
DUPONT
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862
517204
Contents & Storage Conditions:
1 Package Insert, 10 Radiation labels & 2 Vials each containing:
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0mg
Stannous Chloride Dihydrate – 0.075mg
L-Cysteine Hydrochloride Monohydrate – 1.0mg
Sodium Citrate Dihydrate – 2.6mg
Mannitol – 20mg
Store at room temperature (15-30°C)
CONTAINS NO PRESERVATIVES
See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours of reconstitution.
DUPONT
Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI
Sterile
Non-Pyrogenic
Diagnostic Agent for Intravenous Use
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

5 VIAL BOX

Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI

DUPONT

Sterile Non-Pyrogenic
Diagnostic Agent for Intravenous Use

MANUFACTURED BY
E. I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

S17205

CAUTION: Federal (USA) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Contents & Storage Conditions:
1 Package Insert, 10 Radiation labels & 5 Vials each containing:
- Tetrakis (2-methoxy isobutyl isonitrile) Copper (I) tetrafluoroborate – 1.0mg
- Stannous Chloride Dihydrate – 0.075mg
- L-Cysteine Hydrochloride Monohydrate – 1.0mg
- Sodium Citrate Dihydrate – 2.6mg
- Mannitol – 20mg
- Store at room temperature (15-30°C).

CONTAINS NO PRESERVATIVES
See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours of reconstitution.

DUPONT

Cardiolite®
KIT FOR THE PREPARATION OF
TECHNETIUM Tc99m SESTAMIBI

DUPONT

MANUFACTURED BY
E. I. du Pont de Nemours & Co.
Billerica, MA, USA 01862

30 VIAL BOX

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

Cardiolite®

KIT FOR THE PREPARATION OF TECHNETIUM Tc99m SESTAMIBI

Contents & Storage Conditions:
1 Package Insert, 60 Radiation labels & 30 Vials each containing:

- Tetrakis (2-methoxy Isobutyl Isonitrile) Copper (I) tetrafluoroborate – 1.0mg
- Stannous Chloride Dihydrate – 0.075mg
- L-Cysteine Hydrochloride Monohydrate – 1.0mg
- Sodium Citrate Dihydrate – 2.6mg
- Mannitol – 20mg
- Store at room temperature (15-30°C).

CONTAINS NO PRESERVATIVES

See Package Insert for Dosage Information. Reconstitute with additive-free Tc99m and store at room temperature (15-30°C). Use within 6 hours of reconstitution.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use.

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

Tear along perforations
Ready to dispense

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

DUPONT

Cardiolite®

KIT FOR THE PREPARATION OF TECHNETIUM Tc99m SESTAMIBI

CAUTION: Federal (USA) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

S17206

DU PONT

DU PONT DE NEMOURS & COMPANY 05405115

[redacted]

010-000-00234820 DUPONT ACCOUNTS PAYABLE 05405115 02/08/91

VOUCHER NO.	INVOICE NO.	P.O. NUMBER	DATE	GROSS	DISCOUNT	NET
[illegible]75	020191	YDM1223	02-01-91	250.00	.00	250.00
RELEASE:	000027335					
			TOTALS	250.00	.00	250.00

[redacted]

DU PONT

E. I. du Pont de Nemours & Company

INCORPORATED

FINANCE DEPT. - DISBURSEMENTS
WILMINGTON, DELAWARE 19898

05405115

04-1327/611

DATE	CHECK NUMBER	AMOUNT
02/08/91	05405115	$********250.00

PAY TO THE ORDER OF
US GOVT
OFFICE OF THE CONTROLLER
US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

NOT VALID AFTER 90 DAYS

M. T. Sharples

FIRSTATLANTA
The First National Bank of Atlanta
Augusta, Georgia

Better Things for Better Living . . . from Du Pont

⑈05405115⑈ ⑆061113279⑆ 07 519 318⑈

DU PONT

E.I. DU PONT DE NEMOURS & CO. (INC.)
MEDICAL PRODUCTS DEPARTMENT

FEDERAL EXPRESS 3478284031
CUSTOMER PACKAGE TRACKING NUMBER — PULL UP PURPLE TAB

Delivered 8:47 AM 12/10/90
signed by S Stewart

December 7, 1990

United States Nuclear Regulatory Commission
Region I
475 Allendale Road
King of Prussia, PA 19406

Attn.: John D. Kinneman, Chief
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards

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

Gentlemen:

This is a request for an amendment to the above-referenced Reagent Kit Distribution Approval.

As previously communicated to your office, effective January 1, 1991, the name of our company will be changing from Du Pont to the Du Pont Merck Pharmaceutical Company.

Therefore, as of January 1, our name and address should be listed on this approval as:

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

The reagent kits distributed under the authority of this approval will continue to use the Du Pont name after January 1, 1991. Therefore, with this letter we also request authorization to utilize the existing stock of labeling and package inserts with the Du Pont name until the end of the calendar year 1991. Effective on January 1, 1992, all reagent kit product labeling and package inserts will reflect the name of the Du Pont Merck Pharmaceutical Company.

A check is enclosed in the amount of $250.00 in payment of the amendment processing fee specified for License 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
Telephone: (508) 671-8669

DU PONT

E. I. DU PONT DE NEMOURS & COMPANY

05242006

FINANCE DEPT. - DISBURSEMENTS
WILMINGTON, DELAWARE 19898

0-000-002343820 DUPONT ACCOUNTS PAYABLE 05242006 12/03/90

VOUCHER NO.	INVOICE NO.	P.O. NUMBER	DATE	GROSS	DISCOUNT	NET
6537 LEASE:	200032016MD 000018763	YNEN01075	11-27-90	250.00	.00	250.00
TOTALS				250.00	.00	250.00

...NTS PAYABLE

E. I. du Pont de Nemours & Company
INCORPORATED
FINANCE DEPT. - DISBURSEMENTS
WILMINGTON, DELAWARE 19898

05242006

64-1327/611

DATE	CHECK NUMBER	AMOUNT
12/03/90	05242006	$ ********250.00

PAY TO THE ORDER OF
US GOVT
OFFICE OF THE CONTROLLER
US NUCLEAR REGULATORY COMM
WASHINGTON DC 20555

NOT VALID AFTER 90 DAYS

TO FIRSTATLANTA
The First National Bank of Atlanta
Augusta, Georgia

Better Things for Better Living .... from Du Pont

⑈05242006⑈ ⑆061113279⑆ 07 519 318⑈

E.I. DU PONT DE NEMOURS & CO. (INC.)
MEDICAL PRODUCTS DEPARTMENT

April 21, 1988

United States Nuclear Regulatory Commission
Region I
ATTN: John E. Glenn, Ph.D., Chief
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards
475 Allendale Road
King of Prussia, Pennsylvania 19406

Reference: License No. 20-00320-17MA
Docket No. 030-10796
Control No. 108197

Gentlemen:

This is in response to your request for additional information in the letter dated February 19, 1988.

The information required to continue the review of our license amendment request is attached as follows:

1. The letter from the FDA acknowledging receipt of our Notice of Claimed Investigational Exemption for a New Drug (IND 30,612) for the DuPont Reagent Kit RP-217A ("Neurolite TM") for the preparation of Technetium Tc-99m-ECD.

2. The amended preparation instructions that describe the use of the "Caution, Radioactive Material" label around the neck of the vial in step a. on page 6 and the corrected statement on page 7 for NRC approved distribution that properly references Section 35.200 of Title 10 CFR Part 35.

3. A colored copy of the Radiation Label that is applied to the shield.

Please contact me if you require any additional information.

Sincerely,

Francis E. Roy Jr.

Francis E. Roy Jr.
Health Physicist

FER:mr

MEDICAL PRODUCTS DEPARTMENT
331 Treble Cove Road, No. Billerica, MA 01862 Telephone 617-667-9531 Fax (617) 663-7315

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

RECEIVED 9/28/87

IND 30,612

SEP 23 1987

E.I. Dupont de Nemours & Co (Inc.)
Medical Products Department
Diagnostic Imaging Division
331 Treble Cove Road, No.
Billerica, MA 01852

Attention: James R. Weston
Manager, Regulatory Affairs

Dear Sir/~~Madam~~:

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned:	30612
Sponsor:	E.I. Dupont de Nemours & Co. (Inc.)
Name of Drug:	RP-217A, Kit for the Preparation of Technetium Tc99m-ECD
Date of Submission:	September 18, 1987
Date of Receipt:	September 18, 1987

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

FORM FDA 3228a (6/82)

U.S. GOVERNMENT PRINTING OFFICE: 1984-447-553/7405

IND 30,612

Should you have any questions concerning this IND, please call:

Robert L. West
Consumer Safety Officer
(301) 443-4260

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
National Center for Drugs and Biologics (HFN-150)
Attention: DOCUMENT CONTROL ROOM [redacted] #, 9B-23
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Robert L. West for

Director
Division of Oncology and Radiopharmaceutical
Drug Products
National Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228f (6/83)

May 1988

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts 01862

Kit for the Preparation of Technetium Tc99m ECD for Diagnostic Use

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

Vial A -

ECD.2HCl	0.90mg
Stannous chloride, dihydrate	0.072mg (maximum)
Sodium EDTA, dihydrate	0.36mg
Mannitol	24 mg

This vial is lyophilized and stored under nitrogen. The pH of the solution before lyophilization is 2.5 - 2.9. 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.

This vial is stored under air. The pH of vial B 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 Tc99m oxo N,N'-1,2-ethylenediylbis-L-cysteine diethyl ester.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isometric 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 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 ECD (^{99m}Tc complex of N,N' 1,2 ethylenediylbis-L-cysteine 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 ECD 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 ECD 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 ECD. Also, imaging and/or biodistribution studies in seven species show prolonged retention of the agent only in the brains of monkeys. Finally, imaging of the metabolite of Tc99m ECD 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 take up Tc99m ECD 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 15.5 hours.

The primary route of excretion of Tc99m ECD is the urinary and gastrointestinal tracts. On average, 73% of the injected dose is cleared through the bladder during the 24 hours post injection with up to 63% 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 ECD 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 for the next 4-6 hours in order to minimize radiation dose to the bladder.

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

Technetium Tc99m ECD, as well as other radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel and patients.

Technetium Tc99m ECD should be used within six (6) hours after preparation.

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.

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc99m ECD. It is also not known whether Technetium Tc99m ECD 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: None known.

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

185-740MBq (5-20mCi).

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 740MBq (20mCi) of Technetium Tc99m ECD injected intravenously are shown in Table 4.

Table 4. Radiation Absorbed Doses From Tc99m ECD

	Estimated Absorbed Radiation Dose[2] mGy/740 MBq (rads/20 mCi)	
Organ	2.0 Hr. Void	4.8 Hr. Void
Bladder Wall	22.2 (2.2)	54.8 (5.48)
Brain	3.78 (0.38)	3.78 (0.38)
Gallbladder	17.76 (1.78)	18.5 (1.85)
Small Intestine	6.96 (0.7)	7.4 (0.74)
Upper Large Intestine	11.8 (1.18)	12.6 (1.26)
Lower Large Intestine	9.6 (0.96)	11.1 (1.11)
Kidneys	5.6 (0.56)	5.6 (0.56)
Liver	3.55 (0.36)	3.55 (0.36)
Ovaries	4.4 (0.44)	5.92 (0.59)
Red Marrow	1.63 (0.16)	1.92 (0.19)
Testes	1.55 (0.16)	2.66 (0.27)
Lungs	1.4 (0.14)	1.4 (0.14)
Total Body	1.7 (0.17)	2.07 (0.21)

[2]Dosimetry calculated by Oak Ridge Associated Universities.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99M ECD

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

a. Prior to adding the Sodium Pertechnetate Tc99m injection to the 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. With a sterile syringe, inject 1.2ml of Sodium Chloride for Injection into Vial A to dissolve the contents; swirl the contents of the vial for a few seconds.

d. With another sterile syringe, transfer 1ml of Vial A into Vial B.

e. Swirl vial B for a few seconds, and place the vial in a suitable radiation shield appropriately labeled with date, time of preparation, volume and activity.

f. With a sterile shielded syringe, aseptically obtain additive-free sterile, non-pyrogenic sodium pertechnetate Tc99m solution [1.85GBq (50mCi) in 0.5ml].

g. Within five minutes, aseptically add the sodium pertechnetate Tc99m solution to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.

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

i. Examine vial contents for particulates and discoloration prior to injection.

j. Aseptically withdraw required dose using a sterile shielded syringe. Use within six (6) hours of preparation.

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

HOW SUPPLIED: Du Pont's Kit for the Preparation of Technetium Tc99m ECD 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).

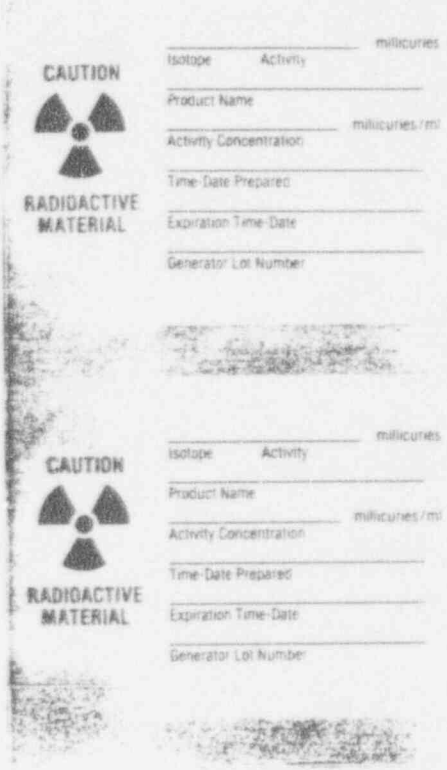
Store at room temperature (15-30°C) after preparation procedure.

This reagent kit is supplied under IND #30,612. "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.

E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 617-482-9595)

512040

Radioactive Material Label
(Lead Shield)



E.I. DU PONT DE NEMOURS & CO. (INC.)
MEDICAL PRODUCTS DEPARTMENT

January 28, 1988

United States Nuclear Regulatory Commission
Region I
Attn: John E. Glenn, Ph.D. Chief
Nuclear Materials Safety Section B
Division of Radiation Safety and Safeguards
631 Park Avenue
King of Prussia, PA 19406

Reference: Approval No. 20-00320-17MA

Gentlemen:

This is a request for renewal of the above-referenced Reagent Kit Distribution Approval.

This renewal application requests authorization to distribute the following DuPont Reagent Kits to persons licensed pursuant to Section 35.14 and Section 35.100, Group III, of 10 CFR Part 35 (effective March 31, 1987) or Section 35.200 of 10 CFR Part 35 (effective April 1, 1987) or under equivalent licenses of Agreement States:

A. "Glucoscan TM" (NDA 17-907)

B. "Pulmolite TM" (NDA 17-776)

C. "Osteolite TM" (NDA 17-972)

D. "Pyrolite TM" (NDA 17-684)

E. "Microlite TM" (NDA 18-263)

F. "Hepatolite TM" (NDA 18-476)

G. "Cardiolite TM" (IND 28,333)

H. "Neurolite TM" (IND 30,612)

This application includes the following information for your review:

1. DuPont, Boston Area Materials License No. 20-00320-21.

2. Reagent Kit documentation segregated by kit name that includes the following:

   a. New drug approval letter (NDA) or acknowledgment of notice (IND) issued by the Food and Drug Administration.

   b. Package insert.

c. Labeling.

d. Packaging.

e. Any applicable and relevant communications to the USNRC.

The communications referenced in Item 2 of the Reagent Kit Distribution Approval that represent the current program and should remain as part of the Approval are included in the appropriate reagent kit section attached to this application. These communications are dated as follows:

1. February 2, 1985

2. March 30, 1987

3. May 19, 1987

The other communications referenced in Item 2 of the Reagent Kit Distribution Approval are superseded by more current information in this application and should be removed from the list. These documents are dated as follows:

1. February 6, 1981

2. March 17, 1982

3. March 22, 1982

4. December 12, 1982

5. June 10, 1983

A check is enclosed in the amount of $700.00 for the renewal application processing fee as specified for Fee Category 3D of Title 10 CFR Part 170, Section 170.31.

Please contact me if you require additional information.

Sincerely,

Francis E. Roy Jr.

FER:mr

NRC FORM 313
(7-87)
10 CFR 30, 32, 33, 34, 35 and 40

U.S. NUCLEAR REGULATORY COMMISSION
APPROVED BY OMB
3150-0120
Expires: 6-30-90

APPLICATION FOR MATERIAL LICENSE

INSTRUCTIONS: SEE THE APPROPRIATE LICENSE APPLICATION GUIDE FOR DETAILED INSTRUCTIONS FOR COMPLETING APPLICATION. SEND TWO COPIES OF THE ENTIRE COMPLETED APPLICATION TO THE NRC OFFICE SPECIFIED BELOW.

APPLICATIONS FOR DISTRIBUTION OF EXEMPT PRODUCTS FILE APPLICATIONS WITH:

U.S. NUCLEAR REGULATORY COMMISSION
DIVISION OF FUEL CYCLE AND MATERIAL SAFETY, NMSS
WASHINGTON, DC 20555

ALL OTHER PERSONS FILE APPLICATIONS AS FOLLOWS, IF YOU ARE LOCATED IN:

CONNECTICUT, DELAWARE, DISTRICT OF COLUMBIA, MAINE, MARYLAND, MASSACHUSETTS, NEW HAMPSHIRE, NEW JERSEY, NEW YORK, PENNSYLVANIA, RHODE ISLAND, OR VERMONT, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION I
NUCLEAR MATERIALS SAFETY SECTION B
631 PARK AVENUE
KING OF PRUSSIA, PA 19406

ALABAMA, FLORIDA, GEORGIA, KENTUCKY, MISSISSIPPI, NORTH CAROLINA, PUERTO RICO, SOUTH CAROLINA, TENNESSEE, VIRGINIA, VIRGIN ISLANDS, OR WEST VIRGINIA, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION II
NUCEAR MATERIALS SAFETY SECTION
101 MARIETTA STREET, SUITE 2900
ATLANTA, GA 30323

IF YOU ARE LOCATED IN:

ILLINOIS, INDIANA, IOWA, MICHIGAN, MINNESOTA, MISSOURI, OHIO, OR WISCONSIN, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION III
MATERIALS LICENSING SECTION
799 ROOSEVELT ROAD
GLEN ELLYN, IL 60137

ARKANSAS, COLORADO, IDAHO, KANSAS, LOUISIANA, MONTANA, NEBRASKA, NEW MEXICO, NORTH DAKOTA, OKLAHOMA, SOUTH DAKOTA, TEXAS, UTAH, OR WYOMING, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION IV
MATERIAL RADIATION PROTECTION SECTION
611 RYAN PLAZA DRIVE, SUITE 1000
ARLINGTON, TX 76011

ALASKA, ARIZONA, CALIFORNIA, HAWAII, NEVADA, OREGON, WASHINGTON, AND U.S. TERRITORIES AND POSSESSIONS IN THE PACIFIC, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION V
NUCLEAR MATERIALS SAFETY SECTION
1450 MARIA LANE, SUITE 210
WALNUT CREEK, CA 94596

PERSONS LOCATED IN AGREEMENT STATES SEND APPLICATIONS TO THE U.S. NUCLEAR REGULATORY COMMISSION ONLY IF THEY WISH TO POSSESS AND USE LICENSED MATERIAL IN STATES SUBJECT TO U.S. NUCLEAR REGULATORY COMMISSION JURISDICTION.

1. THIS IS AN APPLICATION FOR *(Check appropriate item)*

- [ ] A. NEW LICENSE
- [ ] B. AMENDMENT TO LICENSE NUMBER _____
- [X] C. RENEWAL OF LICENSE NUMBER 20-00320-17MA

2. NAME AND MAILING ADDRESS OF APPLICANT *(Include Zip Code)*

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
549 Albany Street
Boston, MA 02118

3. ADDRESS(ES) WHERE LICENSED MATERIAL WILL BE USED OR POSSESSED:

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
331 Treble Cove Road
North Billerica, MA 01862

4. NAME OF PERSON TO BE CONTACTED ABOUT THIS APPLICATION

Francis E. Roy Jr.

TELEPHONE NUMBER

617-671-8242

SUBMIT ITEMS 5 THROUGH 11 ON 8½ x 11" PAPER. THE TYPE AND SCOPE OF INFORMATION TO BE PROVIDED IS DESCRIBED IN THE LICENSE APPLICATION GUIDE.

5. RADIOACTIVE MATERIAL
a. Element and mass number, b. chemical and/or physical form, and c. maximum amount which will be possessed at any one time

6. PURPOSE(S) FOR WHICH LICENSED MATERIAL WILL BE USED

7. INDIVIDUAL(S) RESPONSIBLE FOR RADIATION SAFETY PROGRAM AND THEIR TRAINING AND EXPERIENCE

8. TRAINING FOR INDIVIDUALS WORKING IN OR FREQUENTING RESTRICTED AREAS

9. FACILITIES AND EQUIPMENT

10. RADIATION SAFETY PROGRAM

11. WASTE MANAGEMENT

12. LICENSEE FEES *(See 10 CFR 170 and Section 170.31)*

FEE CATEGORY 3D

AMOUNT ENCLOSED $ 700.00

13. CERTIFICATION. *(Must be completed by applicant)* THE APPLICANT UNDERSTANDS THAT ALL STATEMENTS AND REPRESENTATIONS MADE IN THIS APPLICATION ARE BINDING UPON THE APPLICANT.

THE APPLICANT AND ANY OFFICIAL EXECUTING THIS CERTIFICATION ON BEHALF OF THE APPLICANT, NAMED IN ITEM 2, CERTIFY THAT THIS APPLICATION IS PREPARED IN CONFORMITY WITH TITLE 10, CODE OF FEDERAL REGULATIONS, PARTS 30, 32, 33, 34, 35, AND 40 AND THAT ALL INFORMATION CONTAINED HEREIN, IS TRUE AND CORRECT TO THE BEST OF THEIR KNOWLEDGE AND BELIEF.

WARNING: 18 U.S.C. SECTION 1001 ACT OF JUNE 25, 1948, 62 STAT. 749 MAKES IT A CRIMINAL OFFENSE TO MAKE A WILLFULLY FALSE STATEMENT OR REPRESENTATION TO ANY DEPARTMENT OR AGENCY OF THE UNITED STATES AS TO ANY MATTER WITHIN ITS JURISDICTION.

SIGNATURE–CERTIFYING OFFICER	TYPED/PRINTED NAME	TITLE	DATE
Dennis Dumas	Dennis O. Dumas	Radiation Protection Officer	1/28/88

FOR NRC USE ONLY

TYPE OF FEE	FEE LOG	FEE CATEGORY	COMMENTS	APPROVED BY
AMOUNT RECEIVED	CHECK NUMBER			DATE

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Application Items 5 and 6:

Please reference the attached sections for information on each individual Reagent Kit to be authorized for distribution by this license.

Reagent Kits:

A. "Glucoscan TM" Kit used to prepare Technetium-99m labeled gluceptate sodium.

B. "Pulmolite TM" Kit used to prepare Technetium-99m labeled aggregated albumin.

C. "Osteolite TM" Kit used to prepare Technetium-99m labeled medronate sodium.

D. "Pyrolite TM" Kit used to prepare Technetium-99m labeled pyrophosphate/trimetaphosphate sodium.

E. "Microlite TM" Kit used to prepare Technetium-99m labeled albumin colloid.

F. "Hepatolite TM" Kit used to prepare Technetium-99m labeled Disofenin.

G. "Cardiolite TM" Kit used to prepare Technetium-99m labeled 2-methoxyisobutyl isonitrile.

H. "Neurolite TM" Kit used to prepare Technetium-99m labeled N,N'-1,2-ethylenediylbis-L-cysteine diethyl ester.

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Application Items 7, 8, and 9:

Not Applicable

Application Item 10:

Please reference the DuPont, Boston Area's USNRC Materials License No. 20-00320-21 that is attached to this application as well as the individual sections on each Reagent Kit to be authorized for distribution by this license.

The above-referenced DuPont Boston Area USNRC Materials License is also submitted to demonstrate compliance with the regulatory requirements of Title 10 CFR Part 32, Section 32.73(a)(1).

Application Item 11:

Not Applicable.

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

I. DuPont Boston Area USNRC Materials License No. 20-00320-21.

NRC Form 374
(5-84)

U.S. NUCLEAR REGULATORY COMMISSION

MATERIALS LICENSE

Amendment No. 05

Pursuant to the Atomic Energy Act of 1954, as amended, the Energy Reorganization Act of 1974 (Public Law 93-438), and Title 10, Code of Federal Regulations, Chapter I, Parts 30, 31, 32, 33, 34, 35, 40 and 70, and in reliance on statements and representations heretofore made by the licensee, a license is hereby issued authorizing the licensee to receive, acquire, possess, and transfer byproduct, source, and special nuclear material designated below; to use such material for the purpose(s) and at the place(s) designated below; to deliver or transfer such material to persons authorized to receive it in accordance with the regulations of the applicable Part(s). This license shall be deemed to contain the conditions specified in Section 183 of the Atomic Energy Act of 1954, as amended, and is subject to all applicable rules, regulations and orders of the Nuclear Regulatory Commission now or hereafter in effect and to any conditions specified below.

Licensee	
1. E. I. DuPont de Nemours & Co., Inc. Medical Products Department Boston Area 2. 549 Albany Street Boston, Massachusetts 02118	In accordance with letter received August 6, 1987, 3. License number 20-00320-21 is amended in its entirety to read as follows: 4. Expiration date November 30, 1990 5. Docket or Reference No. 030-28902

6. Byproduct, source, and/or special nuclear material	7. Chemical and/or physical form	8. Maximum amount that licensee may possess at any one time under this license
A. Any byproduct material with atomic numbers 1-83	A. Any	A. 200 curies of each radionuclide with atomic numbers 1 to 83, with a total possession limit of 5,000 curies
B. Krypton 85	B. Any	B. 10,000 curies
C. Molybdenum 99	C. Any	C. 3,000 curies
D. Americium 241	D. Sealed sources	D. 350 curies
E. Xenon 133	E. Any	E. 1,500 curies
F. Nickel 63	F. Any	F. 1,000 curies
G. Sulfur 35	G. Any	G. 1,000 curies
H. Carbon 14	H. Any	H. 1,500 curies
I. Cesium 137	I. Any	I. 500 curies
J. Phosphorus	J. Any	J. 550 curies
K. Strontium 90	K. Any	K. 500 curies
L. Hydrogen 3	L. Any	L. 150,000 curies
M. Any byproduct material with atomic nos. 84-94	M. Any	M. 60 millicuries each radionuclide with atomic nos. 84-94
N. Any byproduct material listed in Schedule B 10 CFR 30.71	N. Any	N. Not to exceed limits specified in Schedule B. 10 CFR 30.71

9. Authorized use

A. through M. (1) Research and Development as defined in Section 30.4(q) of 10 CFR 30.
(2) For possession, use, and processing incident to manufacture of radiochemicals, radiopharmaceuticals and sealed sources.
(3) For storage prior to distribution of manufactured radiochemicals, radiopharmaceuticals and sealed sources.
(4) For packaging and distribution of manufactured radiochemicals, radiopharmaceuticals, and sealed sources to persons authorized to receive the licensed material pursuant to the terms and conditions of specific licenses issued by the Nuclear Regulatory Commission or Agreement States.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 20-00320-21

Docket or Reference number: 030-28902

Amendment No. 05

(Item 9. continued)

(5) For use in calibration of E. I. DuPont NEN Products instruments.
(6) For storage as radioactive wastes.

A. Licensed material possessed at the Boston Site will not exceed 10 Curies per nuclide and 100 Curies total of nuclides with atomic number 3 through 83.

G. Licensed material possessed at the Boston Site will not exceed 200 Curies, S-35. Licensed material possessed at the Westwood Site shall not exceed 400 millicuries, S-35.

H. Licensed material possessed at the Boston Site will not exceed 500 Curies, C-14. Licensed material possessed at the Westwood site shall not exceed 100 millicuries, C-14.

J. Licensed material possessed at the Boston Site will not exceed 90 Curies, P-32. Licensed material possessed at the Westwood Site shall not exceed 150 millicuries, P-32.

L. Licensed material possessed at the Boston Site will not exceed 100,000 Curies, H-3. Licensed material possessed at the Westwood Site shall not exceed 500 millicuries, H-3.

M. Licensed material possessed at the Boston Site will not exceed 50 millicuries per nuclide with atomic numbers 84 through 94.

N. For demonstration by sales persons at customers facilities, anywhere in the United States where the Nuclear Regulatory Commission has jurisdiction.

A. through M. Licensed material possessed at the Billerica Site will not exceed the limits specified after the Boston Site limits are subtracted from the maximum amount.

A. through M. Sealed sources can be returned to the NEN Products, Billerica Site for the purpose of refurbishment or disposal. All such return shipments will be handled in compliance with the conditions of the NEN Products USNRC By-product Materials License, as well as applicable DOT regulations.

CONDITIONS

10. A. Licensed material may be used at the Boston Facility; Building locations at 549, 575, and 609 Albany Street; 100 E. Canton Street; and 120 and 123 E. Dedham Street, Boston, Massachusetts.

B. Licensed material may be used at the Billerica Facility; 331 Treble Cove Road, N. Billerica, Massachusetts. Buildings designated as Nos. 100, 150, 200, 250, 300, 325, 350, 375, 400, 500 and 600.

C. Licensed material in Item 6.N. may be used at and at temporary job sites of the licensee anywhere in the United States where the U. S. Nuclear Regulatory Commission maintains jurisdiction for regulating the use of licensed material.

D. Licensed material as authorized by Items 9.G., 9.H., 9.J. and 9.L. for the Westwood Site may be use at licensee's facilities, 240 University Avenue, Westwood, Massachusetts.

11. A. Licensed material shall be used by, or under the supervision of, individuals designated by the respective Boston or Billerica Site Radioisotope Committee.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number
20-00320-21

Docket or Reference number
030-28902

Amendment No. 05

(11. continued) CONDITIONS

B. The Radiation Protection Officer for the activities authorized by this license is Dennis O. Dumas.

12. This license does not authorize commercial distribution to persons exempt from licensing, to persons generally licensed or for medical use pursuant to Sections 35.14 and 35.31, of 10 Part 35.

13. A(1) Each sealed source or detector cell acquired from another person and containing licensed material, other than hydrogen 3, with a half-life greater than 30 days and in any form other than gas shall be tested for contamination and/or leakage before use. In the absence of a certificate from a transferor indicating that a test has been made within 6 months before the transfer, a sealed source or detector cell received from another person shall not be put into use until tested.

(2) Notwithstanding the periodic leak test required by this condition, any licensed sealed source or detector cell is exempt from such leak tests when the source or detector cell contains 100 microcuries or less of beta and/or gamma emitting materials or 10 microcuries or less of alpha emitting material.

(3) Except for alpha sources, the periodic leak test required by this condition does not apply to sealed sources that are stored and not being used. The sources excepted from this test shall be tested for leakage before any use or transfer to another person unless they have been leak tested within 6 months before the date of use or transfer.

B. Each sealed source or detector cell fabricated by the licensee shall be inspected and tested for construction defects, leakage, and contamination prior to use or transfer as a sealed source or detector cell. If the inspection or test reveals any construction defects or 0.005 microcurie or greater of contamination, the source shall not be used or transferred as a sealed source or detector cell until it has been repaired, decontaminated and retested.

C. Each sealed source containing licensed material, other than hydrogen 3, with a half-life greater than 30 days and in any form other than gas shall be tested for leakage and/or contamination at intervals not to exceed 6 months except that each source designed for the purpose of emitting alpha particles shall be tested at intervals not to exceed 3 months.

D. The test shall be capable of detecting the presence of 0.005 microcurie of radioactive material on the test sample. The test sample shall be taken from the sealed source or detector cell or from the surfaces of the device in which the sealed source or detector cell is permanently or semipermanently mounted or stored on which one might expect contamination to accumulate. Records of leak test results shall be kept in units of microcuries and maintained for inspection by the Commission. Records may be disposed of following Commission inspection.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number
20-00320-21

Docket or Reference number
030-28902

Amendment No. 05

(13. continued) CONDITIONS

E. If the test required by Subsection A. or C. of this condition reveals the presence of 0.005 microcurie or more of removable contamination, the licensee shall immediately withdraw the sealed source or detector cell from use and shall cause it to be decontaminated and repaired or to be disposed of in accordance with Commission regulations. A report shall be filed within 5 days of the date the leak test result is known with the U. S. Nuclear Regulatory Commission, Region I, ATTN: Chief, Nuclear Materials Safety and Safeguards Branch, 631 Park Avenue, King of Prussia, Pennsylvania 19406, describing the equipment involved, the test results, and the corrective action taken.

14. The licensee shall not use licensed material in or on humans beings or in field applications where activity is released except as provided otherwise by specific conditions of this license.

15. Experimental animals administered licensed materials or their products shall not be used for human consumption.

16. A. Detector cells containing titanium tritide foil shall only be used in conjunction with a properly operating temperature control mechanism which prevents foil temperatures from exceeding 225 degrees Centigrade.

B. Detector cells containing scandium tritide foil shall only be used in conjunction with a properly operating temperature control mechanism which prevents foil temperatures from exceeding 325 degrees Centigrade.

17. In lieu of using the conventional radiation caution colors (magenta or purple on yellow background) as provided in Section 20.203(a)(1), of 10 CFR Part 20, the licensee is hereby authorized to label detector cells and cell baths, containing licensed material and used in gas chromatography devices, with conspicuously etched or stamped radiation caution symbols without a color requirement.

18. The licensee may transport licensed material in accordance with the provisions of 10 CFR Part, "Packaging and Transportation of Radioactive Material".

19. Pursuant to Section 20.302, 10 CFR Part 20, the licensee is authorized to exceed the 1 curie limit in Section 20.303(d), 10 CFR Part 20, provided that for the Boston site:

A. Not more than 12 curies total of hydrogen 3 and 1 curie total of all other byproduct material shall be released during any 12 consecutive months, and;

B. All releases to the sewerage system shall be in accordance with the procedures described in the licensee's application dated July 17, 1985, excluding Item 15.J.5. paragraphs 2. and 3.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 20-00320-21

Docket or Reference number: 030-28902

Amendment No. 05

(Continued) CONDITIONS

20. The licensee shall maintain and execute the response measures of his Radiological Contingency Plan for the Boston Site as revised in its entirety dated June, 1985 and attached to letter dated July 26, 1985 and Addendum Item 8 described in letter dated October 16, 1985. The licensee shall also maintain implementing procedures for his Radiological Contingency Plan as necessary to implement the plan. The licensee shall make no change in his Radiological Contingency Plan that would decrease the response effectiveness of the plan without prior Commission approval as evidenced by license amendment. The licensee may make changes to his Radiological Contingency Plan without prior Commission approval if the changes do not decrease the response effectiveness of the plan. The licensee shall maintain records of changes that are made to the Plan without prior approval for a period of two years from the date of the change and shall furnish the Chief, Nuclear Materials Safety and Safeguards Branch, Division of Radiation Safety and Safeguards, U.S. Nuclear Regulatory Commission, Region I, 631 Park Avenue, King of Prussia, Pennsylvania 19406, a report, in duplicate, containing a description of each change with six months after the change is made.

21. A. At the licensee's Boston Site no more than 15 curies of phosphorus-32 shall be used or stored in any building unless radiation detection systems and alarms to continuously monitor possible effluent releases are installed and operated.

B. Notwithstanding the requirements of Condition A above; the licensee is not required to comply with Condition 21.A. with respect to phosphorus-32 wastes stored in non-combustible drums when the drums are porvided with sprinkler protection.

22. The licensee shall maintain and execute the response measures of his Radiological Contingency Plan for the Billerica Site as revised in its entirety dated June, 1985, and attached to letter dated July 26, 1985. The licensee shall also maintain implementing procedures for his Radiological Contingency Plan as necessary to implement the Plan. The licensee shall make no change in his Radiological Contingency Plan that would decrease the response effectiveness of the plan without prior Commission approval as evidenced by license amendment. The licensee may make changes to his Radiological Contingency Plan without prior Commission approval if the changes do not decrease the response effectiveness of the plan. The licensee shall maintain records of changes that are made to the Plan without approval for a period of two years from the date of the change and shall furnish the Chief, Nuclear Materials Safety and Safeguards Branch, Division of Radiation Safety and Safeguards, U.S. Nuclear Regulatory Commission, Region I, 631 Park Avenue, King of Prussia, Pennsylvania 19406, a report, in duplicate, containing a description of each change within six months after the change is made.

MATERIALS LICENSE
SUPPLEMENTARY SHEET

License number: 20-00320-21

Docket or Reference number: 030-28902

Amendment No. 05

(Continued) CONDITIONS

23. The licensee may possess up to 10 curies of Iodine-125 waste in any building at the Billerica Site without installation of radiation detection systems and alarms to continuously monitor possible effluent releases from associated ventilation systems, provided, the material is stored as waste in non-combustible drums and the drums are provided with sprinkler protection.

25. Except as specifically provided otherwise in this license, the licensee shall conduct its program in accordance with the statements, representations, and procedures contained in the documents including any enclosures, listed below. The Nuclear Regulatory Commission's regulations shall govern unless the statements, representations and procedures in the licensee's application and correspondence are more restrictive than the regulations.

A. Letter dated December 17, 1984
B. Application dated July 17, 1985
C. Letter dated October 16, 1985
D. Letter dated January 21, 1986
E. Letter dated September 12, 1986
F. Letter received February 5, 1987
G. Letter dated June 29, 1987
H. Letter dated August 6, 1987
I. Letter dated August 26, 1987

For the U.S. Nuclear Regulatory Commission

Date 17 SEP 1987

By Original Signed By:
Jenny M. Johansen
Nuclear Materials Safety and
Safeguards Branch, Region 1
King of Prussia, Pennsylvania 19406

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

A. "Glucoscan TM" (NDA 17-907)

SENDER: Complete items 1, 2, and 3.
Add your address in the

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

MAY 25 1978

NDA 17-907

New England Nuclear
Attention: Mr. William T. Brown
Atomlight Place
North Billerica, Massachusetts 01862

DRUG REGULATORY AFFAIRS

MAY 30 1978

Dear Mr. Brown:

We are pleased to acknowledge the receipt on April 7, 1978, of your communication dated April 6, 1978 enclosing printed labeling pursuant to your new drug application for GLUCOSCAN (Technetium Tc 99m Gluceptate Sodium Kit).

The application was filed on April 7, 1978.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. However, it is understood from the discussion by telephone on May 5, 1977 between your representative, Ms. Linda Drachman, and Nathan R. Rosenthal, Ph.D. of this Administration that at the next printing of the package insert, or within six months of your receipt of this letter you will make the following revision:

> In Table 2. Technetium Tc 99m Physical Decay Chart; Half-Life 6.02 hours you will limit this to 8 hours in accord with the expiration time of the radioactive preparation as stated elsewhere in the labeling.

It was further understood that adjustment of the nonradioactive kit to pH 9.0 provides the conditions needed to obtain a pH in the finished radioactive dosage form of 5.5 to 7.5, as proposed on page 8-128 of the original application.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the kit when available.

Sincerely yours,

M. J. Finkel

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures: Records & Reports Requirements (Reg. 310.300)
Conditions of Approval of NDA

PACKAGE INSERT

March 1987

USA & CANADA
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, MA, USA 01862

GLUCOSCAN®

Kit for the Preparation of Technetium Tc99m Gluceptate

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Gluceptate Sodium - 200mg
Stannous Chloride, minimum ($SnCl_2.2H_2O$) - 0.06mg
Total Tin, maximum - 0.07mg

Prior to lyophilization the pH is adjusted to between 8.5-9.1 with HCl and/or NaOH. The contents of the vial are lyophilized and contain no bacteriostatic preservative.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxident-free Sodium Pertechnetate Tc99m Injection.

The precise structure of stannous technetium-gluceptate complex is unknown at this time.

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

	Mean Energy

VIAL LABEL

511773

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30ºC). Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

GLUCOSCAN®

Kit for the preparation of Technetium Tc 99m Gluceptate

CONTENTS & STORAGE CONDITIONS
Gluceptate Sodium - 200mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.08mg
Total Tin, maximum - 0.07mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30ºC).
CAUTION: Federal (USA) law prohibits dispensing without prescription. Rx
U.K. PL/5848/0001 REG-NR. 1360189 CANADIAN LICENSE #145

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription. RSR

Technetium Tc 99m Gluceptate

Contents
Gluceptate sodium - 200mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum - 0.07mg

Use within 6 hours.

Tc 99m_____

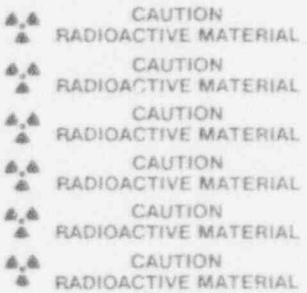
Activity Concentration Volume

Time/Date Prepared

Expiration Time Lot No.
511779

RADIOACTIVE MATERIAL LABEL

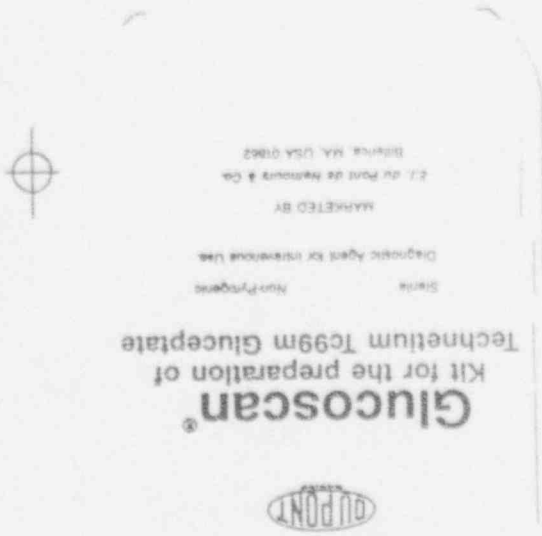
(Neck of vial with final radioactive preparation)



Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

PACKAGING



CAUTION: Federal (USA) law prohibits dispensing without prescription. PCM

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS & STORAGE CONDITIONS:

1 Package Insert, 12 Radiation Labels, and 5 Vials, each containing:

- Gluceptate Sodium - 200mg
- Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 5.06mg
- Total Tin, maximum - 0.07mg
- The pH is adjusted with HCl and/or NaOH.
- Store at room temperature (15-30°C).
- CONTAINS NO PRESERVATIVE.

See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30°C). Use within 6 hours.

DUPONT

Glucoscan®

Kit for the preparation of Technetium Tc99m Gluceptate

Canadian License #145
German Reg.Nr. 1360189
U.K.PL/5849/0001

DUPONT

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

PACKAGING

DUPONT

GLUCOSCAN®

Kit for the preparation of Technetium Tc99m Gluceptate

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

GLUCOSCAN®
Kit for the preparation of
Technetium Tc99m Gluceptate

DUPONT

DUPONT

GLUCOSCAN®
Kit for the preparation of
Technetium Tc99m Gluceptate

Contents & Storage Conditions:
1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:
Gluceptate Sodium - 200mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.06mg
Total Tin, maximum - 0.07mg

The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See package insert for dosage information. Reconstitute with additive free ^{99m}Tc and store at room temperature (15-30°C). Use within 6 hours.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

E. I. du Pont de Nemours & Co.

DUPONT

(maximum six vials)

CAUTION: Federal (USA) law prohibits dispensing without prescription. Rx only
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Canadian License # 145
German Reg-Nr. 1360189
U.K. PL/5849/0001

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Tear along perforations
Ready to dispense

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

517178

Open this end for Package Insert and Radiation Labels

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

B. "Pulmolite TM" (NDA 17-776)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NOV 18 1976

NDA 17-776

DRUG REGULATORY
AFFAIRS

NOV 18 1976

New England Nuclear
Attention: Linda Drachman
Atomlight Place
North Billerica, Massachusetts 01862

Gentlemen:

Reference is made to your new drug application dated August 22, 1975, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Pulmolite (Technetium Tc 99m Aggregated Albumin Kit).

We also acknowledge receipt of your additional communications dated August 19, September 8, and October 5, 12, and 18, 1976, providing final printed labeling.

The application was filed on October 20, 1976.

We have completed the review of this application as amended and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

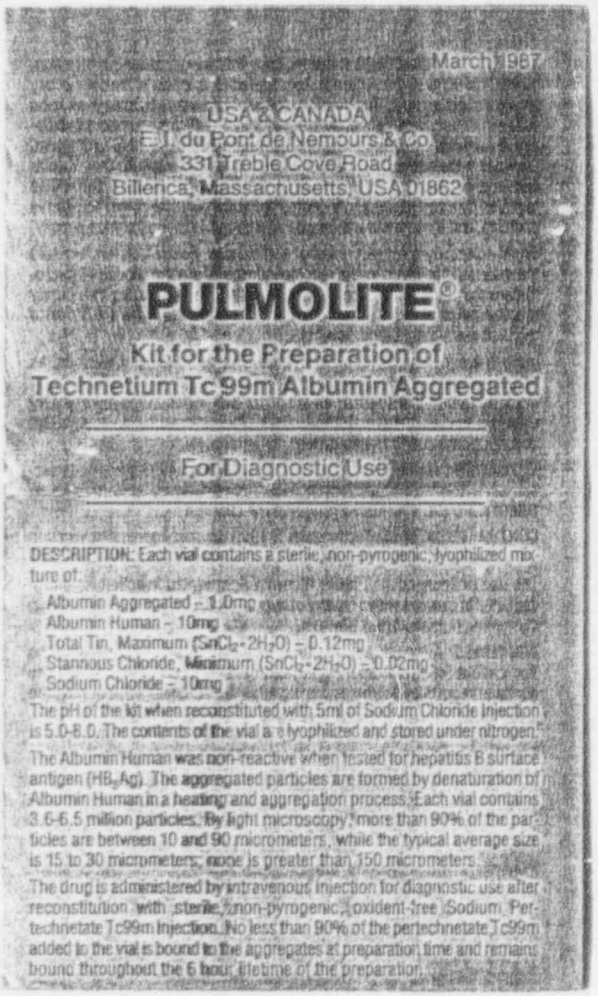
Sincerely yours,

Marion J. Finkel

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of NDA

PACKAGE INSERT



March 1987

USA & CANADA
E. I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

PULMOLITE®

Kit for the Preparation of Technetium Tc 99m Albumin Aggregated

For Diagnostic Use

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Albumin Aggregated – 1.0mg
Albumin Human – 10mg
Total Tin, Maximum ($SnCl_2 \cdot 2H_2O$) – 0.12mg
Stannous Chloride, Minimum ($SnCl_2 \cdot 2H_2O$) – 0.02mg
Sodium Chloride – 10mg

The pH of the kit when reconstituted with 5ml of Sodium Chloride Injection is 5.0-8.0. The contents of the vial are lyophilized and stored under nitrogen. The Albumin Human was non-reactive when tested for hepatitis B surface antigen (HB_sAg). The aggregated particles are formed by denaturation of Albumin Human in a heating and aggregation process. Each vial contains 3.6-6.5 million particles. By light microscopy, more than 90% of the particles are between 10 and 90 micrometers, while the typical average size is 15 to 30 micrometers; none is greater than 150 micrometers.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxident-free Sodium Pertechnetate Tc99m Injection. No less than 90% of the pertechnetate Tc99m added to the vial is bound to the aggregates at preparation time and remains bound throughout the 6 hour lifetime of the preparation.

VIAL LABEL

511777

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at 2-8°C. Use within 6 hours. CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

PULMOLITE®

Kit for the preparation of Technetium Tc 99m Albumin Aggregated

CONTENTS & STORAGE CONDITIONS

Albumin Aggregated - 1.0mg
Albumin Human - 10mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.12mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg
Sodium Chloride - 10mg
Store at room temperature (15-30°C). Protect from light.

CAUTION: Federal (USA) law prohibits dispensing without prescription. (RX)

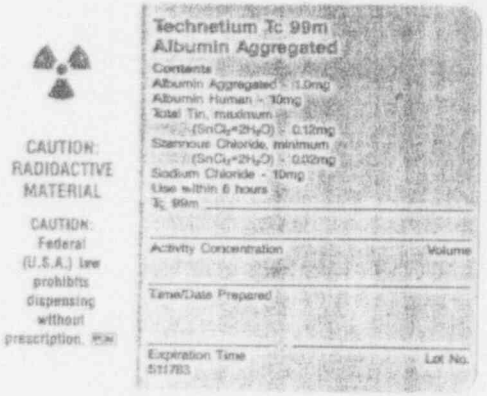
U.K. PL/5849/0005 REG-NR. 0291492 CANADIAN LICENSE #145

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)



RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

PULMOLITE®
Kit for the preparation of
Technetium Tc99m Albumin Aggregated

DUPONT

CAUTION: Federal (USA) law prohibits dispensing without prescription. (POM)
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS & STORAGE CONDITIONS
1 Package Insert, 12 Transfer Labels, and 5 Vials, each containing:
Albumin Aggregated - 1.0mg
Albumin Human - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.02mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.12mg
Sodium Chloride - 10mg
Store at room temperature (15-30°C). Protect from light.
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at 2-8°C. Use within 6 hours.

DUPONT

PULMOLITE®

Kit for the preparation of
Technetium Tc99m Albumin Aggregated

Canadian License #145
German Reg-Nr. 0291492
U.K.PL/5849/0005

DUPONT

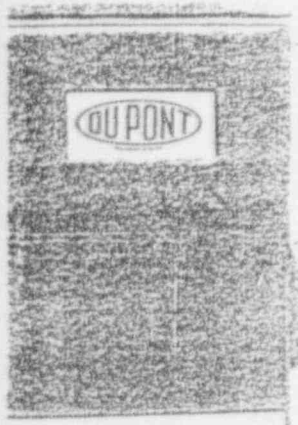
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA. USA 01862

DUPONT

PULMOLITE®

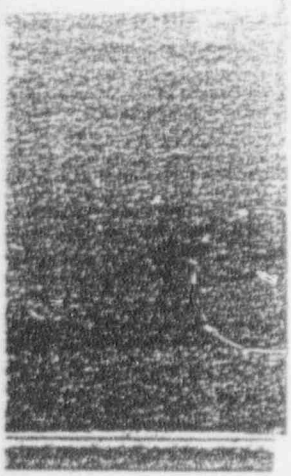
Kit for the preparation of
Technetium Tc99m Albumin Aggregated

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862



Contents & Storage Conditions
1 Package Insert, 72 Radiation Labels and
30 vials, each containing:
Albumin Aggregated - 1mg
Albumin Human - 10mg
Stannous Chloride, minimum
$SnCl_2 \cdot 2H_2O$) - 0.02mg
maximum
$SnCl_2 \cdot 2H_2O$) - 0.12mg
Store at room temperature (15-30°C).
Protect from light.
CONTAINS NO PRESERVATIVE.

See package insert for dosage information.
Reconstitute with additive free Tc99m and store
at 2-8°C. Use within 6 hours.



CONVENIENCE PACK

DUPONT

PULMOLITE®
Kit for the preparation of
Technetium Tc99m Albumin Aggregated

Sterile Non-Pyrogenic
Diagnostic Agent for Intravenous Use

E. I. du Pont de Nemours & Co.

DUPONT

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
Inside Bottom Flap

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

517184

DUPONT

PULMOLITE®
Kit for the preparation of
Technetium Tc99m Albumin Aggregated

CAUTION: Federal (USA) law prohibits dispensing without prescription. [Rx Only]
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Canadian License # 145
German Reg-Nr. 0291492
U.K. PL/5849/0005

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Open this end for Package Insert
and Radiation Labels.

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

C. "Osteolite TM" (NDA 17-972)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20857

DEC 1 9 1977

NDA 17-972

DRUG REGULATORY
AFFAIRS

DEC 21 1977

New England Nuclear
Radiopharmceutical Division
Attention: L. Drachman
Atomlight Place
North Billerica, Massachusetts 01862

Gentlemen:

We are pleased to acknowledge the receipt on November 7, 1977, of your communication dated November 4, 1977, enclosing printed labeling pursuant to your new drug application for Osteolite™ (Technetium Tc 99m Medronate Sodium Kit).

The application was filed on November 7, 1977.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

M J. Finkel

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of NDA

PACKAGE INSERT

March 1987

USA & CANADA
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts, USA 01862

OSTEOLITE®

Kit for the Preparation of Technetium Tc99m Medronate

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Medronate Disodium – 10mg
Total Stannous and Stannic Chloride – 4mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) – 0.5mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) – 1.15mg

Prior to lyophilization, the pH is adjusted to between 7.0-7.5 with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

Administration is administered by intravenous injection for diagnostic use, after reconstitution with sterile, non-pyrogenic, oxidant-free Sodium Pertechnetate Tc99m injection.

The precise structure of stannous technetium medronate complex is known at this time (JACS Vol. 102, 2476, 1980).

PHYSICAL CHARACTERISTICS

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

Table 1. Principal Radiation Emission Data

VIAL LABEL

511775

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30ºC). Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

OSTEOLITE®

Kit for the preparation of Technetium Tc 99m Medronate

CONTENTS & STORAGE CONDITIONS
Medronate Disodium - 10mg
Total Stannous and Stannic Chloride - 1mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.5mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.15mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30ºC).
Lyophilized and stored under nitrogen.
CAUTION: Federal (USA) law prohibits dispensing without prescription. ℞
U.K. PL/58/90004 REG-NR. 0291552 CANADIAN LICENSE #145
MARKETED by
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription. Rx only

Technetium Tc 99m Medronate

Contents
Medronate Disodium - 10mg
Total Stannous and Stannic Chloride - 1mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.5mg
Total Tin, maximum
($SnCl_2 \cdot 2H_2O$) - 1.15mg
Use within 6 hours.

Tc 99m _____ _____

Activity Concentration Volume

Time/Date Prepared

Expiration Time Lot No.
511782

RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL
CAUTION
RADIOACTIVE MATERIAL
CAUTION
RADIOACTIVE MATERIAL
CAUTION
RADIOACTIVE MATERIAL
CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

PACKAGING

DUPONT

OSTEOLITE®

Kit for the preparation of
Technetium Tc99m Medronate

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

OSTEOLITE®
Kit for the preparation of
Technetium Tc99m Medronate

DUPONT

DUPONT

DUPONT

OSTEOLITE®
Kit for the preparation of
Technetium Tc99m Medronate

Contents & Storage Conditions

1 Package Insert, 72 Radiation Labels and 30 vials, each containing:
Medronate Disodium ... 10mg
Stannous Chloride, minimum
$(SnCl_2 \cdot 2H_2O)$ ... 0.5mg
Total Tin, maximum
$(SnCl_2 \cdot 2H_2O)$ ... 1.15mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See package insert for dosage information. Reconstitute with additive free ^{99m}Tc and store at room temperature (15-30°C). Use within 6 hours.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

CONVENIENT
← RE-ORDER POINT
(maximum fifteen vials)

E. I. du Pont de Nemours & Co.

DUPONT

← (maximum six vials)

CAUTION: Federal (USA) law prohibits dispensing without prescription. Rx only.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Canadian License # 145
German Reg-Nr. 0291552
U.K. PL/5849/0004

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Tear along perforations
Ready to dispense

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

517180

Open this end for Package Insert
and Radiation Labels

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

D. "Pyrolite TM" (NDA 17-684)

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
ROCKVILLE, MARYLAND 20852

NDA 17-684

NOV 19 1976

New England Nuclear
Radiopharmaceutical Division
Attention: Linda Drachman
Atomlight Place
North Billerica, Massachusetts 01862

Gentlemen:

Reference is made to your new drug application dated April 30, 1976, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Pyrolite (Stannous Pyrophosphate/ Trimetaphosphate Agent).

We also acknowledge the receipt of your additional communications dated July 30, 1976, amending the application, and October 4 and 12, 1976, providing final printed labeling.

The application was filed on October 13, 1976.

It is understood from the discussion by telephone on November 4, 1976, between your representative, Mrs. Linda Drachman, and Mrs. Kathleen Jongedyk of this Administration that a series of minor revisions in the labels and labeling will be instituted at the next printing or within six months, whichever is sooner.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

M J Finkel

Marion J. Finkel, M.D.
Associate Director for
New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirement (Reg. 310.300)
Conditions of Approval of NDA

PACKAGE INSERT

March 1987

USA & CANADA
E.I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862

PYROLITE®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$)-0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$)-1.8mg

Prior to lyophilization the pH is adjusted to between 4.5-5.5 with HCl and/or NaOH. The contents of the vial are lyophilized, stored under nitrogen and contain no bacteriostatic preservative.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxident-free Sodium Pertechnetate Tc99m Injection or isotonic saline.

The precise chemical structure of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates is unknown at this time.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours. Photons that are useful for detection and imaging studies

VIAL LABEL

511778

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30°C). Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

PYROLITE®

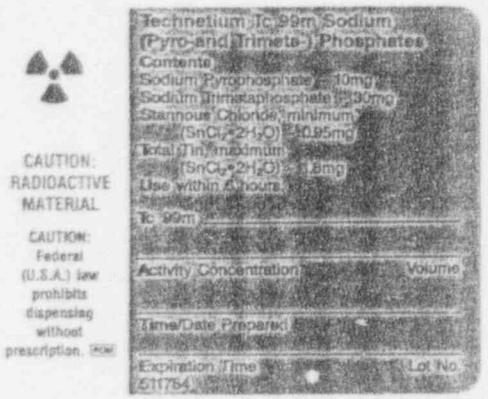
Kit for the preparation of Technetium Tc 99m Sodium (Pyro- and Trimeta-) Phosphates

CONTENTS & STORAGE CONDITIONS
Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
Lyophilized and stored under nitrogen.
CAUTION: Federal (USA) law prohibits dispensing without prescription.
U.K. PL/5849/0006 REG-NR. 029612 CANADIAN LICENSE #146
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)



RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

PYROLITE®

Kit for the preparation of
Technetium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

MARKETED BY

E. I. du Pont de Nemours & Co.

Billerica, MA, USA 01862

CAUTION: Federal (USA) law prohibits dispensing without prescription. PUM

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS & STORAGE CONDITIONS:

1 Package Insert, 12 Radiation Labels, and 5 Vials, each containing:

- Sodium Pyrophosphate - 10mg
- Sodium Trimetaphosphate - 30mg
- Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.95mg
- Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 1.8mg
- The pH is adjusted with HCl and/or NaOH.
- Store at room temperature (15-30ºC).
- CONTAINS NO PRESERVATIVE

See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30ºC). Use within 6 hours.

PYROLITE®

Kit for the preparation of
Technetium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

Canadian License #145
German Reg-Nr. 0291612
U.K.PL/5849/0006

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

DUPONT

PYROLITE®

Kit for the preparation of Technetium Tc99m Sodium (Pyro- and Trimeta-) Phosphates

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

PACKAGING

DUPONT

PYROLITE®
Kit for the preparation of
Tectir · tium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

DUPONT

PYROLITE®
Kit for the preparation of
Technetium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

DUPONT

DUPONT

PYROLITE®
Kit for the preparation of
Technetium Tc99m Sodium
(Pyro- and Trimeta-) Phosphates

Contents & Storage Conditions:

1 Package Insert, 20 Radiation Labels and 30 Vials, each containing:
Sodium Pyrophosphate - 10mg
Sodium Trimetaphosphate - 30mg
Stannous Chloride, maximum
$(SnCl_2 \cdot 2H_2O)$ - 0.95mg
Total Tin, maximum
$(SnO_2 \cdot 2H_2O)$ - 1.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C).
CONTAINS NO PRESERVATIVE.

See package insert for dosage information. Reconstitute with additive free ^{99m}Tc and store at room temperature (15-30°C). Use within 6 hours.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use.

CONVENIENT
← RE-ORDER POINT
(maximum fifteen vials)

E. I. du Pont de Nemours & Co.

DUPONT

← (maximum six vials)

CAUTION: Federal (USA) law prohibits dispensing without prescription. Rx only

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Canadian License # 145
German Reg-Nr. 0291612
U.K. PL/5849/0006

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Tear along perforations
Ready to dispense.

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

517188

Open this end for Package Insert and Radiation Labels

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

E. "Microlite TM" (NDA 18-263)

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-263

MAR 25 1983

New England Nuclear
Attention: Ms. S. Flint
Medical Diagnostic Division
601 Treble Cove Road
N. Billerica, MA 01862

RECEIVED 3/29/83

Dear Ms. Flint:

Please refer to your new drug application dated January 31, 1979 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Microlite (Technetium Tc 99m Albumin Colloid). This application was resubmitted on August 13, 1980, October 9, 1981 and July 21, 1982.

The application was filed on February 18, 1983.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

In the next six months or the next printing of the package insert (whichever occurs first) we request that you make the following changes.

Please replace Table 4 with the following:

TABLE 4 RADIATION DOSES*

Tissue	Radiation Absorbed Dose (rads/8 mCi)
Liver	2.72
Spleen	1.68
Red marrow	0.22
Testes	0.01
Ovaries	0.045
Total Body	0.15

Method of Calculation "S", Absorbed Dose Per Unit Cumulated Activity for Selected Radionuclides and Organs, MIRD Pamphlet No. 11 (1975).

*Assumes distribution, retention identical to Tc 99m Sulfur Colloid.

Please submit one market package of the drug when available.

Sincerely yours,

Robert Temple

Robert Temple, M.D
Acting Director
Office of New Drug Evaluation
National Center for Drugs and Biologics

Enclosures: Records and Reports Requirement (Reg. 310.300)

5-195

PACKAGE INSERT

September 1987

USA & CANADA
E.I du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, MA, USA 01862

MICROLITE®

Kit for the preparation of Technetium Tc99m Albumin Colloid

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.006mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg
Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg

MICROLITE®, Kit for the preparation of Technetium Tc99m Albumin Colloid is prepared from Albumin that was nonreactive when tested for hepatitis B antigen (HB_sAG).

Prior to lyophilization the pH is adjusted with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

The 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 stannous technetium-albumin colloid complex is unknown at this time.

PHYSICAL CHARACTERISTICS

VIAL LABEL

511776

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at 2-8°C. Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

MICROLITE®

Kit for the preparation of Technetium Tc 99m Albumin Colloid

CONTENTS & STORAGE CONDITIONS

Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.066mg
Poloxamer 188 - 1.1mg, Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg
Store at room temperature (15-30°C). Protect from light.
CAUTION: Federal (USA) law prohibits dispensing without prescription. ℞

U.K. PL/5849/0003 REG-NR. 0291658 CANADIAN LICENSE #145

MARKETED BY
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription. Rx

Technetium Tc 99m
Albumin Colloid

Contents
Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Stannous Chloride, minimum
($SnCl_2 \cdot 2H_2O$) - 0.206mg
Total Tin, maximum
($SnCl_2 \cdot 2H_2O$) - 0.17mg
Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg
Sodium Pyrophate (Anhydrous) - 10mg
Use within 6 hours.

Tc 99m

Activity Concentration — Volume

Time/Date Prepared

Expiration Time — Lot No.

511781

RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

MARKETED BY

E.I. du Pont de Nemours & Co.

MICROLITE®

Kit for the preparation of

Technetium Tc99m Albumin Colloid

DU PONT

CAUTION: Federal (USA) law prohibits dispensing without prescription. POM

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS & STORAGE CONDITIONS:

1 Package Insert, 12 Radiation Labels, and 5 Vials, each containing:

- Albumin Colloid - 1mg
- Normal Human Serum Albumin - 10mg
- Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.006mg
- Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.17mg
- Poloxamer 188 - 1.1mg
- Medronate Disodium - 0.12mg
- Sodium Phosphate (Anhydrous) - 10mg

Store at room temperature (15-30°C). Protect from light.

CONTAINS NO PRESERVATIVE

See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at 2-8°C. Use within 6 hours.

DU PONT

MICROLITE®

Kit for the preparation of

Technetium Tc99m Albumin Colloid

Canadian License #145

U.K.PL/5849/0003

German Reg-Nr. 0291658

DU PONT

Marketed By

E.I. du Pont de Nemours & Co.

Billerica, Massachusetts, USA 01862

PACKAGING

DUPONT

MICROLITE®

Kit for the preparation of
Technetium Tc99m Albumin Colloid

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

MICROLITE®
Kit for the preparation of
Technetium Tc99m Albumin Colloid

DUPONT

MICROLITE®
Kit for the preparation of
Technetium Tc99m Albumin Colloid

Contents & Storage Conditions:

1 Package Insert, 72 Radiation Labels and 30 Vials, each containing:
Albumin Colloid - 1mg
Normal Human Serum Albumin - 10mg
Stannous Chloride, maximum
$(SnCl_2 \cdot 2H_2O)$ - 0.006mg
Total Tin, maximum
$(SnCl_2 \cdot 2H_2O)$ - 0.17mg
Poloxamer 188 - 1.1mg
Medronate Disodium - 0.12mg
Sodium Phosphate (Anhydrous) - 10mg
Store at room temperature (15-30°C).
Protect from light.
CONTAINS NO PRESERVATIVE.

See package insert for dosage information. Reconstitute with additive free Tc99m and store at 2-8°C. Use within 6 hours.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

CAUTION: federal (USA) law prohibits dispensing without prescription. POM

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

← CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

E. I. du Pont de Nemours & Co.

DUPONT

Canadian License # 145
German Reg-Nr. 0291658
U.K. PL/5849/0003

← (maximum six vials)

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

517182

Open this end for Package Insert and Radiation Labels.

E.I. DU PONT DE NEMOURS & CO. (INC.)
BIOMEDICAL PRODUCTS DEPARTMENT

02 February 1985

John Glenn, Ph.D.
U.S. Nuclear Regulatory
Commission, Region I
631 Park Avenue
King of Prussia, PA 19406

RE: License Approval No. 20-00320-17MA
Amendment No. 10, MICROLITE™ Kit
for Use in the Preparation of
Technetium Tc99m Albumin Colloid.

REF: RA/MDR/NDA/07/85

Dear Dr. Glenn:

By this communication, E.I. DuPont de Nemours and Co. (Inc.), NEN Medical Products (formerly New England Nuclear Corporation) is submitting final printed labeling (FPL) as part of its license amendment for the product MICROLITE™, Kit for Use in the Preparation of Technetium Tc99m Albumin Colloid. This is in reference to the above license approval dated 19 July 1983, and to correspondence dated 15 July 1983 with control number 04622 (copies enclosed).

This labeling is the current product labeling and is believed to comply with all NRC requirements; it has been approved by the U.S. Food and Drug Administration.

Submission of this FPL in duplicate is believed to complete any and all outstanding issues relating to the NRC license amendment for this product. Please contact us if you have any additional questions.

Sincerely,

Dennis Dumas
Area Supervisor
Safety & Environmental Affairs

DD/jc
Enclosures

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

REAGENT KIT DISTRIBUTION APPROVAL

NEW ENGLAND NUCLEAR CORPORATION

NEN MEDICAL DIAGNOSTIC DIVISION
549 ALBANY STREET
BOSTON, MASSACHUSETTS 02118

Approval No. 20-00320-17MA
Amendment No. 10

In accordance with letter dated June 10, 1983, Approval Number 20-00320-17MA is amended as follows:

Subitem 1.G. is amended to read:

Kit Trade Name	Radiopharmaceutical Prepared From Kit
G. "Microlite TM" Technetium 99m Microaggregated Albumin Kit (NDA 18-263)	G. Technetium 99m labeled albumin colloid

Item 2. is amended to read:

The reagent kit(s) listed above shall be manufactured, packaged, labeled, and distributed in accordance with statements, representations and procedures contained in letters dated February 6, 1981, March 17, 1982, March 22, 1982, December 12, 1982, and June 10, 1983.

FOR THE U. S. NUCLEAR REGULATORY COMMISSION

Original Signed by
JOSEPH DELMEDICO

Date JUL 19 1983

By Material Licensing Branch
Division of Fuel Cycle and Material Safety
Washington, D. C. 20555

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D. C. 20555

July 15, 1983

FCMLB:JD
030-10796
(15093)

New England Nuclear Corporation
ATTN: Dennis Dumas
Operational Safety and
Environmental Control
549 Albany Street
Boston, Massachusetts 02118

Gentlemen:

In order to avoid further delays in the marketing of your "Microlite TM" product, we are amending your Reagent Kit Distribution Approval No. 20-00320-17MA as expeditiously as possible. We note; however, that the product labeling does not completely fulfill the commitments that you made in your letter dated December 10, 1982 (copy enclosed). Please note the following:

1. Under 10 CFR 20.203(f), the NRC licensee who reconstitutes a reagent kit is required to label the kit reaction vial. The label that is placed on the lead shield surrounding the vial does not fulfill this requirement if the vial can accidentally become separated from the shield.

   In addition to the labels that the manufacturer supplies for the lead shield that surrounds the reaction vial, we believe that the manufacturer should supply labels, and directions to complete and affix them, that are adequate to fulfill the requirements of 10 CFR 20.203(f). After reconstitution, the vial labeling must include a radiation caution symbol of the design and colors specified in Section 20.203 (magenta or purple on a yellow background), the words "CAUTION, RADIOACTIVE MATERIAL", and identification of the radioactive contents.

2. The kit preparation procedures should be modified to include instructions substantially similar to the following:

   a. Complete and affix the radiation warning label to the reaction vial. (See Item 1. above.)

b. Place the reaction vial in a suitable lead shield that has a fitted lead cap.

c. Use a shielded syringe when introducing the pertechnetate solution into the reaction vial.

d. Place the lead cap on the vial shield prior to mixing the contents by swirling, inversion, etc.

e. Maintain adequate shielding during ther life of the product by using the lead vial shield with lead cap in place and by using a syringe shield for withdrawing and injecting the preparation.

f. Complete and affix the vial shield label supplied with the kit.

We recognize that changes of this type may have to be coordinated with other agencies, printers, etc. In addition, you may wish to use up existing stocks of package inserts or hold these changes until a major revision of the package insert is undertaken. So that we may complete our record on your amendment, please submit a draft of the changes that you will make and indicate (or estimate) the anticipated future date that these changes can be incorporated into the package insert.

Please reply in duplicate and refer to Control No. 04622.

Sincerely,

Joseph DelMedico

Joseph DelMedico
Material Licensing Branch
Division of Fuel Cycle ar
Material Safety

Enclosure:
NEN ltr. dtd. 12/10/82

PACKAGE INSERT

May 1984

NEN MEDICAL PRODUCTS
331 Treble Cove Road
North Billerica, Massachusetts 01862

MICROLITE™

Kit for use in the preparation of Technetium Tc 99m Albumin Colloid

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial of MICROLITE™ Kit for use in the preparation of Technetium Tc 99m Albumin Colloid contains a sterile, pyrogen-free, lyophilized mixture of 1mg albumin colloid, 10mg normal human serum albumin, 0.17mg (maximum) total tin (as stannous chloride $SnCl_2 2H_2O$), 0.006mg (minimum) stannous chloride ($SnCl_2 2H_2O$), 1.1mg poloxamer 188, 0.12mg medronate disodium and 10mg sodium phosphate (anhydrous). MICROLITE™ Kit for use in the preparation of Technetium Tc 99m Albumin Colloid is prepared from albumin that was nonreactive when tested for hepatitis B antigen (HB_sAg) by radioimmunoassay. Prior to lyophilization the pH is adjusted with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

Administration is by intravenous injection for diagnostic use, after reconstitution with sodium pertechnetate Tc 99m injection. The product as supplied is sterile and pyrogen-free.

The precise structure of stannous technetium-albumin colloid complex is unknown at this time.

PHYSICAL CHARACTERISTICS

Technetium Tc 99m decays by isomeric transition with a physical half life of 6.02 hours.[1] Photons that are useful for detection and imaging studies are listed in Table 1.

Table 1. Principal Radiation Emission Data

Radiation	Mean n_p/Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

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

EXTERNAL RADIATION

The specific gamma ray constant for Tc 99m is 5.4 microcoulombs/kg MBq-hr (0.78R/millicurie-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 Pb is shown in Table 2. To facilitate control of the radiation exposure from MBq (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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

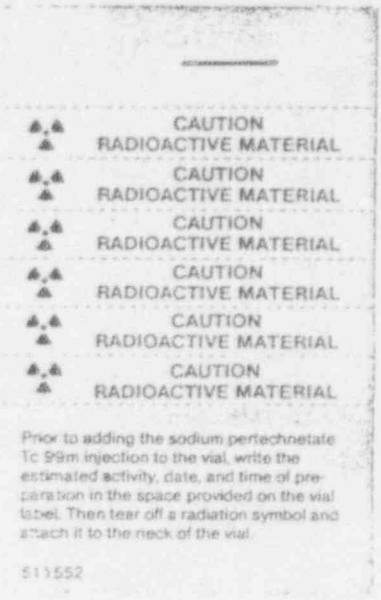
Hours	Fraction Remaining	Hours	Fraction Remaining
0*	1.000	7	.447
1	.891	8	.398
2	.794	9	.355
3	.708	10	.316
4	.631	11	.282
5	.562	12	.251
6	.501		

* Calibration Time

VIAL LABEL


Format 9132 18
MICROLITE™
CONTENTS
Lot No. 1231
Exp. Date 1 Sep. 85
NEN Medical Products
DUPONT
PMS 4205 Blue
Medium Varnish

RADIATION LABEL (VIAL)



RADIATION LABEL (LEAD SHIELD)

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

CAUTION:
RADIOACTIVE
MATERIAL

CAUTION:
Federal
(U.S.A.) law
prohibits
dispensing
without
prescription.

Technetium Tc 99m
Albumin Colloid

511555

CONTENTS:
Albumin Colloid – 1mg
Normal Human Serum Albumin – 10mg
Total Tin, maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
Poloxamer 188 – 1.1mg
Medronate Disodium – 0.12mg
Sodium Phosphate (Anhydrous) – 10mg
Sodium Pertechnetate Tc 99m ______ mCi

______ mCi/ml
Activity Concentration

Time/Date Prepared

Expiration Time

1517156

DUPONT

NEN Medical Products

MICROLITE™

Kit for use in the preparation of
Technetium Tc 99m Albumin Colloid

See enclosed Package Insert
Diagnostic Agent for Intravenous Injection.
Use as directed.
Catalog Number NRP-470
Sterile Non-Pyrogenic
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Marketed by
NEN Medical Products
331 Treble Cove Rd.
North Billerica, Mass. 01862

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radionuclides.

Contents: 1 Package Insert, 12 Radiation Labels and 5 vials, each containing:

- Albumin Colloid – 1mg
- Normal Human Serum Albumin – 10mg
- Total Tin, Maximum (as Stannous Chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
- Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (Minimum) – 0.006mg
- Poloxamer 188 – 1.1mg
- Medronate Disodium – 0.12mg
- Sodium Phosphate (Anhydrous) – 10mg

Store at room temperature (15°-30°C) before reconstitution. Prior to use lyophilized vials should be protected from light. CONTAINS NO BACTERIOSTAT.

For intravenous use after reconstitution in accordance with the directions supplied. Use additive-free Technetium Tc 99m. Please see the Package Insert. After reconstitution store at 2-8°C and use within 6 hours.

DUPONT

MICROLITE™

Kit for use in the preparation of
Technetium Tc 99m Albumin Colloid

Catalog Number NRP-470

DUPONT

NEN Medical Products

Marketed by
NEN Medical Products
North Billerica, MA 01862

DUPONT

MICROLITE™

Kit for use in the preparation of Technetium Tc 99m Albumin Colloid

Catalog Number NRP-470C

Marketed by
NEN Medical Products
331 Treble Cove Road
North Billerica, MA 01862

CONVENIENCE PACK

DUPONT

MICROLITE™
Kit for use in the preparation of
Technetium Tc 99m Albumin Colloid

DUPONT

MICROLITE™
Kit for use in the preparation of
Technetium Tc 99m Albumin Colloid

DUPONT

MICROLITE™
Kit for use in the preparation of
Technetium Tc 99m Albumin Colloid

CONTENTS:
1 Package Insert, 72 Radiation labels and 30 vials, each containing:
- Albumin Colloid – 1mg
- Normal Human Serum Albumin – 10mg
- Total Tin, maximum (as stannous chloride $SnCl_2 \cdot 2H_2O$) – 0.17mg
- Stannous Chloride ($SnCl_2 \cdot 2H_2O$) (minimum) – 0.006mg
- Poloxamer 188 – 1.1mg
- Medronate Disodium – 0.12mg
- Sodium Phosphate (Anhydrous) – 10mg

Store at room temperature (15°-30°C) before reconstitution. Prior to use lyophilized vials should be protected from light.

CONTAINS NO BACTERIOSTAT.

For intravenous use after reconstitution in accordance with the directions supplied. Use additive free Technetium Tc 99m. Please see the Package Insert. After reconstitution store at 2-8°C and use within 6 hours.

Diagnostic Agent for Intravenous Injection.
Use as directed.

Catalog Number NRP-470C

Sterile Non-Pyrogenic

CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

CONVENIENT
REORDER POINT
(Maximum fifteen vials)

DUPONT

NEN Medical Products

(Maximum six vials)

Catalog Number NRP-470C

Sterile Non-Pyrogenic

CAUTION: Federal (U.S.A.) law pro
dispensing without prescription.
IMPORTANT: Read enclosed Pac
Insert for full information on prepar
use and indications.
WARNINGS: Radiopharmaceutica
should be used by persons who ar
qualified by specific training in the
use and handling of radionuclides
duced by nuclear reactor or particl
celerator and whose experience ar
training have been approved by the
propriate governmental agency auth
to license the use of radionuclides.

Marketed by
NEN Medical Products
North Billerica, MA 01862

Tear along perforations
Ready to dispense.

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed by
NEN Medical Products
North Billerica, MA 01862

517157

Open this end for Package
Insert and Radiation Labels

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

F. "Hepatolite TM" (NDA 18-467)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 18-467

New England Nuclear
Attention: Ms. Susan Flint
601 Treble Cove Road
North Billerica, MA 01862

Rec'd RA
3/17/82

Gentlemen:

Please refer to your new drug application dated February 27, 1980 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Hepatolite (Technetium Tc 99m Disofenin Kit). This application was resubmitted on January 19, 1981 and July 17, 1981.

We also acknowledge receipt of your additional communication dated March 3, 1982.

The application was filed on February 16, 1982.

We have completed the review of this application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved.

The enclosures summarize the conditions relating to the approval of this application.

Please submit one market package of the drug when available.

Sincerely yours,

M. J. Finkel, M.D.

Marion J. Finkel
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirement (Reg 310.300)
Conditions of Approval of NDA

PACKAGE INSERT

March 1987

USA & CANADA
E. I. du Pont de Nemours & Co.
331 Treble Cove Road
Billerica, Massachusetts USA 01862

HEPATOLITE®

Kit for the Preparation of Technetium Tc99m Disofenin

FOR DIAGNOSTIC USE

DESCRIPTION: Each vial contains a sterile, non-pyrogenic, lyophilized mixture of:

Disofenin 20mg
Stannous Chloride, maximum ($SnCl_2 \cdot 2H_2O$) 0.24mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) 0.6mg

Prior to lyophilization the pH is adjusted to between 4-5 with HCl and/or NaOH. The contents of the vial are lyophilized and stored under nitrogen.

The drug is administered by intravenous injection for diagnostic use after reconstitution with sterile, non-pyrogenic, oxident-free Sodium Pertechnetate Tc99m injection.

The structure of disofenin is shown below:

The precise structure of stannous technetium-disofenin complex is unknown at this time.

PHYSICAL CHARACTERISTICS:

VIAL LABEL

511774

Tc 99m Activity _____
Time/Date Prepared _____
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30°C). Use within 6 hours.
CONTAINS NO PRESERVATIVE.

Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use

HEPATOLITE®

Kit for the preparation of Technetium Tc 99m Disofenin

CONTENTS & STORAGE CONDITIONS
Disofenin - 20mg
Stannous Chloride, minimum ($SnCl_2 \cdot 2H_2O$) - 0.24mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) - 0.8mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C). Protect from light.
Lyophilized and stored under nitrogen.

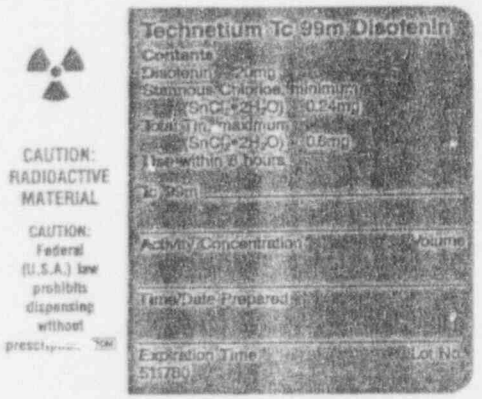
CAUTION: Federal (USA) law prohibits dispensing without prescription.
U.K. PL/0849/0002 REG-NR. 0291575 CANADIAN LICENSE #145
MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

(DUPONT)

Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Lead Shield)



RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

CAUTION
RADIOACTIVE MATERIAL

Prior to adding the sodium pertechnetate Tc 99m injection to the 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.

511552

PACKAG

517185

CAUTION: Federal (USA) law prohibits dispensing without prescription. [POM]
IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.
WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

CONTENTS & STORAGE CONDITIONS:
1 Package Insert, 12 Radiation Labels, and 5 Vials, each containing:
Disofenin ... 20mg
Stannous Chloride, monohydr. ($SnCl_2 \cdot 2H_2O$) ... 0.24mg
Total Tin, maximum ($SnCl_2 \cdot 2H_2O$) ... 0.5mg
The pH is adjusted with HCl and/or NaOH.
Store at room temperature (15-30°C). Protect from light.
CONTAINS NO PRESERVATIVE.
See Package Insert for dosage information. Reconstitute with additive-free Tc 99m and store at room temperature (15-30°C). Use within 6 hours.

DUPONT

HEPATOLITE®

Kit for the preparation of
Technetium Tc99m Disofenin

Canadian License #145
German Reg-Nr. 0291575
U.K. PU5849/0002

DUPONT

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA. USA 01862

HEPATOLITE®
Kit for the preparation of
Technetium Tc99m Disofenin

Sterile Non-Pyrogenic
Diagnostic Agent for Intravenous Use

MARKETED BY
E.I. du Pont de Nemours & Co.
Billerica, MA. USA 01862

PACKAGING

DUPONT

HEPATOLITE®

Kit for the preparation of
Technetium Tc99m Disofenin

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

CONVENIENCE PACK

DUPONT

HEPATOLITE®
Kit for the preparation of
Technetium Tc99m Disofenin

DUPONT

HEPATOLITE®
Kit for the preparation of
Technetium Tc99m Disofenin

Contents & Storage Conditions

- Package Insert, 72 Radiation Labels and 30 Vials, each containing:

Disofenin 20mg
Stannous Chloride, minimum
$(SnCl_2 \cdot 2H_2O)$ 0.22mg
Total Tin, maximum
$(SnCl_2 \cdot 2H_2O)$ 2.6mg
The pH is adjusted with HCl and/or NaOH
Store at room temperature (15-30°C)
Protect from light
CONTAINS NO PRESERVATIVE

See package insert for dosage information. Reconstitute with additive free Tc99m and store at room temperature (15-30°C). Use within 6 hours.

Sterile Non-Pyrogenic

Diagnostic Agent for Intravenous Use

E. I. du Pont de Nemours & Co.

DUPONT

CONVENIENT
RE-ORDER POINT
(maximum fifteen vials)

(maximum six vials)

CAUTION: Federal (USA) law prohibits dispensing without prescription. RX ONLY

IMPORTANT: Read enclosed Package Insert for full information on preparation, use and indications.

WARNING: Radiopharmaceuticals should be used by persons who are qualified by specific training 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.

Canadian License # 145
German Reg-Nr. 0291575
U.K. PL/5849/0002

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

Tear along perforations.
Ready to dispense.

Package Insert and Radiation Labels
Inside Bottom Flap

Marketed By
E. I. du Pont de Nemours & Co.
Billerica, Massachusetts, USA 01862

5/1/86

Open this end for Package Insert
and Radiation Labels

E.I. DuPont de Nemours & Co., Inc.
Medical Products Department
Boston Area

Application for Material License

Attachments

II. Reagent Kits

G. "Cardiolite TM" (IND 28,333)

Fil
RP-30

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

MAY 12 1986

IND 28,333

Dupont Diagnostic Imaging
Division
331 Treble Cove Road Rt.
Billerica Ma. 01862
Attn J.D. Bernardy

5/19/86
R.T.

Dear Sir

We are pleased to acknowledge receipt of your Notice of Claimed Investigational Exemption for a New Drug (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act. Please note the following identifying data:

IND Number Assigned: 28,333

Sponsor: Dupont Diagnostic Imaging Division

Name of Drug: Tc 99m RP 30 for myocardial imaging

Date of Submission: May 7, 1986

Date of Receipt: May 8, 1986

IT IS UNDERSTOOD THAT STUDIES IN HUMANS WILL NOT BE INITIATED UNTIL 30 DAYS AFTER THE DATE OF RECEIPT SHOWN ABOVE. If, within the 30 day period, we notify you of serious deficiencies that require correction before human studies can begin or that would require restriction of human studies until correction, it is understood that you will continue to withhold or restrict such studies until you are notified that the material you have submitted to correct the deficiencies is satisfactory.

You are responsible for compliance with the Federal Food, Drug, and Cosmetic Act and Regulations. This responsibility includes the immediate reporting of any alarming reactions in either animal or human studies, and submission of progress reports at intervals not to exceed one year.

IND 28,393

Should you have any questions concerning this IND, please call:

Mr. Mark Anderson
Consumer Safety Officer
(301) 443-4460

Please forward all future communications concerning this IND in TRIPLICATE IDENTIFIED with this IND NUMBER and addressed as follows:

Food and Drug Administration
National Center for Drugs and Biologics(HFN-150)
Attention: DOCUMENT CONTROL ROOM # ~~1B-28~~ 9135
5600 Fishers Lane
Rockville, Maryland 20857

Sincerely yours,

Mark Anderson for

Director
Division of Oncology and Radiopharmaceutical
Drug Products
National Center for Drugs and Biologics

CC:
Orig. File - pink
Division File - yellow
Division CSO - blue

ACKNOWLEDGEMENT

FORM FDA 3228! (6/83)

DOMESTIC

December 1986

E.I. du Pont de Nemours & Co.
Diagnostic Imaging Division
331 Treble Cove Road
N. Billerica, Massachusetts 01862

CARDIOLITE™
Kit for the preparation of
TECHNETIUM Tc99m Hexamibi
for Diagnostic Use

DESCRIPTION: Each vial contains 1mg of $[Cu(MIBI)_4]BF_4$ (Where MIBI = 2-methoxy isobutyl isonitrile); 0.075mg stannous chloride, dihydrate; 1mg L-cysteine hydrochloride, monohydrate; 2.6mg sodium citrate, dihydrate; and 20mg mannitol. The pH is 5.3 to 5.9 prior to lyophilization. The contents of the vial are lyophilized and stored under nitrogen.

This drug is administered by intravenous injection for diagnostic use after reacting with sodium pertechnetate Tc99m injection. The precise structure of the technetium complex is $Tc99m[MIBI]_6^+$ where MIBI is 2-methoxyisobutyl isonitrile.

PHYSICAL CHARACTERISTICS

Technetium Tc99m decays by isomeric transition with a physical half-life of 6.02 hours (1). Photons that are useful for 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 Pb is shown in Table 2. To facilitate control of the radiation exposure from Megabequerel (millicurie) amounts of this radionuclide, the use of a 0.25cm thickness of Pb will attenuate the radiation emitted 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; Tc99m Half-Life 6.02 Hours.

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

*Calibration Time

CLINICAL PHARMACOLOGY: Tc99m Hexamibi is a cationic Tc99m complex which has been found to accumulate in viable myocardial tissue in proportion to regional blood flow, analogous to thallous chloride Tl-201. Animal cross-over experiments using, Tl-201 and Tc99m Hexamibi have confirmed that the myocardial distribution of Tc99m Hexamibi correlates well with regional myocardial perfusion.

Scintigraphic images obtained in animals and man after the intravenous administration of Tc99m Hexamibi have been comparable to those obtained with Tl-201 in normal, infarcted and transiently ischemic myocardial tissue.

The major metabolic pathway for clearance of Tc99m Hexamibi is the hepatobiliary system. Activity from the gall bladder appears in the intestines within one hour of injection. Twenty percent of the injected dose is cleared through the renal elimination in 24 hours. The agent is excreted without any evidence of metabolism.

Pulmonary activity is negligible even immediately after injection. Blood clearance studies indicate that eighty percent of the injected dose clears with a $t_{1/2}$ of 1.5 to 1.9 minutes at stress and rest respectively. At five minutes post injection about 8% of the injected dose remains in circulation. The myocardial $t_{1/2}$ is approximately six hours, rest and stress, while the $t_{1/2}$ for the liver is 1.2 hours after a rest injection and 2.5 hours after a stress injection. The ideal imaging time, reflecting the best compromise between heart count rat and contrast, is approximately 1-2 hours after a rest injection and 1/2-2 hours after a stress injection. There is no evidence for change in myocardial distribution (redistribution), therefore imaging at delayed times is possible.

Myocardial uptake which is coronary flow dependent is 2.8% of the injected dose. Animal studies have shown that uptake is not blocked when the sodium pump mechanism is inhibited. However, hypoxia reduces the level of myocardial extraction. Animal studies have also indicated that ischemic tissues do not exhibit normal extraction for up to five hours after the stress event.

INDICATIONS AND USAGE: Technetium Tc99m Hexamibi may be useful in the diagnosis and localization of myocardial infarction.

Technetium Tc99m Hexamibi may be useful in conjunction with exercise stress testing as an adjunct in the diagnosis of ischemic heart disease.

Technetium Tc99m Hexamibi may be useful in the assessment of global ventricular function.

CONTRAINDICATIONS: None known.

WARNINGS: In studying patients in whom cardiac disease is known or suspected, care should be taken to assure continuous monitoring and treatment in accordance with safe, accepted clinical procedure. Exercise stress testing should only be performed under the supervision of a qualified physician and in a laboratory equipped with the appropriate support and resuscitation apparatus.

PRECAUTIONS: Contents of the vial are intended only for use in the preparation of Technetium Tc99m Hexamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

Technetium Tc99m Hexamibi, as well as other radioactive drugs must be handled with care and appropriate safety measures should be used to minimize radiation exposure to clinical personnel and patients.

Technetium Tc99m Hexamibi should be be used within six (6) hours after preparation.

Carcinogenesis, Mutagenesis, Impairment of Fertility

No long term animal studies have been performed to evaluate carcinogenic potential. A normal and a sensitized Ames test has demonstrated no mutagenic changes induced by exposure to Technetium Tc99m Hexamibi.

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

ADVERSE REACTIONS: No adverse reactions specifically attributable to the use of Technetium Tc99m Hexamibi have been reported.

DOSAGE AND ADMINISTRATION: The suggested dose range for intravenous administration, after preparation with oxidant-free sodium pertechnetate Tc99m injection, in the average patient (70 kg) is 370-1110MBq (10-30mCi). The patient dose should be measured by a suitable radioactivity calibration system just prior to 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.

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

Table 4. Radiation Absorbed Doses from Tc99m Hexamibi

	Estimated Radiation Absorbed Dose			
	STRESS		REST	
Organ	Rads/30mCi	mGy/1110MBq	Rads/30mCi	mGy/1110MBq
Bladder	1.65	16.5	2.34	23.4
Small Intestine	0.20	2.0	0.30	3.0
Upper Large Intestine Wall	0.20	2.0	0.39	3.9
Lower Large Intestine Wall	0.22	2.2	0.36	3.6
Gallbladder	0.19	1.9	0.19	1.9
Heart Wall	0.78	7.8	0.81	8.1
Kidneys	1.29	12.9	2.46	24.6
Liver	0.29	2.9	0.39	3.9
Lungs	0.57	5.7	0.57	5.7
Spleen	0.63	6.3	0.75	7.5
Thyroid	1.71	17.1	2.85	28.5
Ovaries	0.23	2.3	0.27	2.7
Testes	0.14	1.4	0.14	1.4
Red Marrow	0.25	2.5	0.25	2.5
Total Body	0.18	1.8	0.19	1.9

HOW SUPPLIED: Du Pont's CARDIOLITEyH* Kit for the preparation of Technetium Tc99m Hexamibi Kit is supplied in kits of ten (10) vials, sterile and pyrogen-free, each vial containing in lyophilized form:

$[Cu(MIBI)_4]BF_4$	1.0mg
Stannous Chloride, Dihydrate	0.075mg
Mannitol	20.0mg
Sodium Citrate, Dihydrate	2.6mg
L-Cysteine Hydrochloride, Monohydrate	1.0mg

The pH is between 5.3-5.9 prior to lyophilization. The contents of the vial are lyophilized and stored under nitrogen. Store at room temperature (15-30°) before and after reconstitution. Technetium Tc99m Hexamibi contains no perservatives. Protect from light. Included in each ten (10) vial kit is one (1) product monograph and twelve (12) radiation labels.

The components of the Kit for the preparation of Tc99m Hexamibi are supplied sterile and non-pyrogenic. Aseptic procedures normally used in making additions and withdrawals from sterile, non-pyrogenic containers should be used during addition of pertechnetate solution and the withdrawal of doses for patient administration.

Technetium Tc99m Hexamibi is prepared by adding no more than 2.78GBq (75mCi) of additive-free non-pyrogenic Sodium Pertechnetate Tc99m Injection in 1-3ml to the vial and boiling for ten minutes. Appropriate shielding should be used during the preparation of the Technetium Tc99m Hexamibi.

INSTRUCTIONS FOR PREPARATION OF TECHNETIUM Tc99m Hexamibi

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

1. Waterproof gloves should be worn during the preparation procedure. Remove the plastic disc from the vial and swab the top of the vial closure with alcohol to sanitize the surface.
2. Place the vial in a suitable radiation shield with a fitted radiation cap.
3. With a sterile shielded syringe, aseptically obtain additive-free, sterile, non-pyrogenic Sodium Pertechnetate Tc99m Injection to the vial. [max. 2.78GBq (75mCi)] in approximately 1 to 3ml.
4. Aseptically add the sodium pertechnetate Tc99m Injection to the vial in the lead shield. Without withdrawing the needle, remove an equal volume of headspace to maintain atmospheric pressure within the vial.
5. Swirl the contents of the vial for a few seconds.
6. Place the vial with the lead shield upright in a boiling water bath for 10 minutes. Timing for 10 minutes is begun as soon as the water begins to boil again.
7. Remove the shielded vial from the water bath and allow to cool for fifteen minutes.

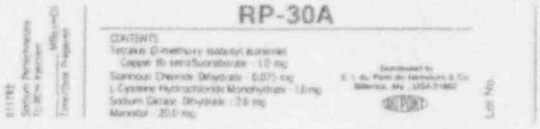
8. Using proper shielding, the vial containing the reconstituted solution should be visually inspected for particulates and/or discoloration prior to injection.
9. Complete and affix the "radioactive contents" label to the vial shield.
10. Aseptically withdraw material for use within six (6) hours. Store reconstituted vial at room temperature (15-30°C). The vial contains no preservative.

This reagent kit is supplied under IND #28-333. This reagent kit is approved by the U.S. Nuclear Regulatory Commission for distribution to persons licensed pursuant to Sections 35.14 and 35.100, Group III, of 10 CFR Part 35, or under equivalent licenses of Agreement States.

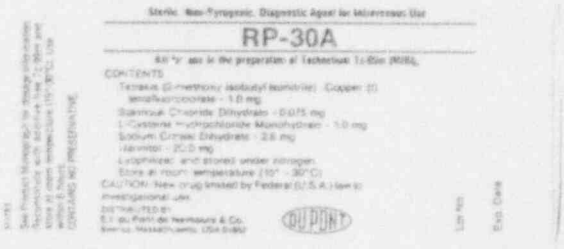
E.I. du Pont de Nemours & Co.
Diagnostic Imaging Division
331 Treble Cove Road
North Billerica, Massachusetts 01862
Tel: Toll Free 800-225-1572
(For Massachusetts and International, call 617-482-9595)

511846

VIAL LABEL

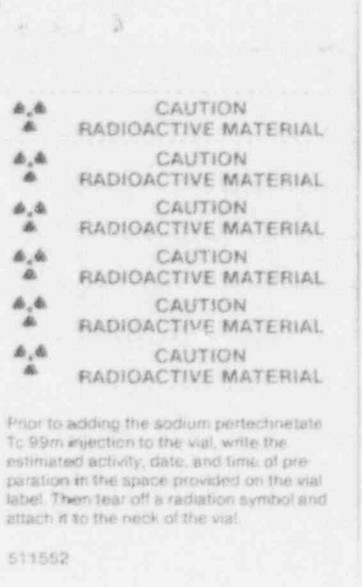


BOX LABEL


Sterile, Non-Pyrogenic, Diagnostic Agent for Intravenous Use
RP-30A
Kit "A" use in the preparation of Technetium Tc-99m (NDA)
CONTENTS
Tetrakis (2-methoxy isobutyl isonitrile) Copper (I)
tetrafluoroborate - 1.0 mg
Stannous Chloride Dihydrate - 0.075 mg
L-Cysteine Hydrochloride Monohydrate - 1.0 mg
Sodium Citrate Dihydrate - 2.6 mg
Mannitol - 20.0 mg
Lyophilized and stored under nitrogen.
Store at room temperature (15° - 30°C).
CAUTION: New drug limited by Federal (U.S.A.) law to
investigational use.
DISTRIBUTED BY:
E.I. du Pont de Nemours & Co.
DUPONT
Lot No.
Exp. Date

RADIOACTIVE MATERIAL LABEL

(Neck of vial with final radioactive preparation)



BETWEEN:

LICENSE FEE MANAGEMENT BRANCH, ARM
AND
REGIONAL LICENSING SECTIONS

(FOR LFMS USE)
INFORMATION FROM LTS

PROGRAM CODE: 02512
STATUS CODE: 2
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: 930601
DOCKET NO: 3010796
CONTROL NO.: 118167
LICENSE NO.: 20-00320-17MA
ACTION TYPE: RENEWAL

2. FEE ATTACHED
AMOUNT: $540.00
CHECK NO.: 00885006

3. COMMENTS

SIGNED Rebecca J. Brown
DATE 6/17/93

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE 03 IS ENTERED / 6/1)

1. FEE CATEGORY AND AMOUNT: 3D $540

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
AMENDMENT /
RENEWAL ----------
LICENSE ----------

3. OTHER ----------

SIGNED ----------
DATE 6/29/93