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. 19

In accordance with letter dated November 2, 1992, Approval No 20-00320-17MA is amended in its entirely to read as follows:

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Pharmaceutical Company to persons licensed pursuant to Section 35.14 and Section 35.100, Group III, of 10 CFR Part 35, (superseded) or Section 35.11 and Section 35.200 of 10 CFR Part 35 (effective April 1, 1987) or under equivalent licenses of Agreement States.

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

G.	"Cardiolite TM" Technetium 99m (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, packages, labeled, and distributed in accordance with statements, representations and procedures contained in letters dated January 28, 1988, April 21, 1988, December 7, 1990, March 13, 1991, January 15, 1992, and June 19, 1992, October 6, 1992 and November 2, 1992.

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

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

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

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

For the U.S. Nuclear Regulatory Commission

Date JAN 05 1993

By Original Signed By:
Elizabeth Ullrich

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

JAN 05 1993

License No. 20-00320-17MA
Docket No. 030-10796
Control No. 117392

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

Dear Mr. Roy:

Please find enclosed an amendment to your NRC Material License.

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

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

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

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

OFFICIAL RECORD COPY - G:\WPS\MLTR\L2000320.17A - 12/29/92

ML 10

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

Sincerely,

Original Signed By:
Elizabeth Ulrich

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

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

DRSS:RI
Dolce/gc
~~12/ /92~~
1/4/93

DRSS:RI
Kinneman
1/5/93

CONVERSATION RECORD

TIME 1:35pm | DATE 12/23/92

TYPE ☐ VISIT ☐ CONFERENCE ☒ TELEPHONE ☐ INCOMING ☒ OUTGOING

Location of Visit/Conference:

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

ROUTING

NAME/SYMBOL	INT

SUBJECT

Approval # 20-00320-17MA
Amendment # [redacted]19

SUMMARY

① Address: Post office North Billerica or Billerica? ← location

② Tc 99m Sestamibi - separate line item or keep it w/ "G"?

pts insert expanded to include treatment for ischemia → no other changes

③ Change item G to read:

"Cardiolite TM" Technetium 99m Sestamibi
Technetium 99m
(IND 28,253) (NDA-19-785

ACTION REQUIRED

Revised amendment 19.

NAME OF PERSON DOCUMENTING CONVERSATION	SIGNATURE	DATE
DOLCE	K Dolce	12/23/92

ACTION TAKEN

SIGNATURE	TITLE	DATE

OFFICIAL RECORD COPY ML 10 1/7392

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

030-10796

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.
Development Health Physicist

Log [illegible]
Remitter [illegible]
Check No. [illegible]
Amount $330
Fee Category 3D
Type of Fee AMD
Date Check Rec'd [illegible]
Date Completed [illegible]
By: [illegible]

OFFICIAL RECORD COPY ML 10

117392

NOV 03 1992

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

4. Store the reaction vial containing the Technetium Tc99m Sestamibi at 15-25°C (59-77°F) prior to use. At each 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.

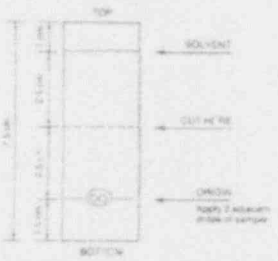
Final product with radiochemical purity of at least 90% was used in the clinical trials that established safety and effectiveness. The radiochemical purity was determined by the following method.

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 3-4cm. 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), 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)

513062

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 $SnCl_2 \cdot 2H_2O$) - 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	88.07	140.5

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/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 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 ischemic 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 injection 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 4.5 minutes at rest, and clears with a $t_{1/2}$ of 1.6 minutes under exercise conditions. At five minutes post injection about 6% 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 minutes	1.2	1.2	19.6	19.4	1.5	1.5	5.9	5.8
30 minutes	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	0.9	2.2	1.7	1.2	1.0	0.5	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 test modes.

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 to 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 occured 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 procedure 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-month acute cardiac patients) were:

Fatigue	30%
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 iodomediate, $[Cu(MIBI)_4]BF_4$, 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 (≥22µg/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 can test systemic and bone marrow toxicity (5mg/kg, > 500 × 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 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 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:

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			
	2.0 hour void		4.8 hour void	
Organ	rads/ 30mCi	mGy/ 1110MBq	rads/ 30mCi	mGy/ 1110MBq
Breasts	0.7	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	3.8	40.0	4.2	41.1
Stomach Wall	0.6	6.1	0.6	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	4.8	0.5	4.8

	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	1.9
Gallbladder Wall	2.8	28.9	2.8	27.6
Small Intestine	2.4	24.4	2.4	24.4
Upper Large Intestine Wall	4.3	44.4	4.5	44.4
Lower Large Intestine Wall	3.3	30.2	3.3	30.2
Stomach Wall	0.5	5.3	0.5	5.2
Heart Wall	0.5	5.6	0.5	5.5
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	4.5
Urinary Bladder Wall	3.9	35.5	9.7	90.0
Total Body	0.4	4.2	0.4	4.2

Radiation Pharmaceutical Internal Dose Information Center, July, 1990, Oak Ridge Associated Universities, P.O. Box 117, Oak Ridge, TN 37831, (615) 576-3446.

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 filled 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.

BETWEEN:

LICENSE FEE MANAGEMENT BRANCH, ARM
AND
REGIONAL LICENSING SECTIONS

(FOR LFMS USE)
INFORMATION FROM LTS

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

LICENSE FEE TRANSMITTAL

A. REGION

1. APPLICATION ATTACHED
APPLICANT/LICENSEE: DU PONT MERCK PHARMACEUTICAL CO.
RECEIVED DATE: 921103
DOCKET NO: 30-0796
CONTROL NO.: 117392
LICENSE NO.: 20-00320-17MA
ACTION TYPE: AMENDMENT

2. FEE ATTACHED
AMOUNT: $330.00
CHECK NO.: 50313821

3. COMMENTS

SIGNED Rebecca J. Brown
DATE 11/5/92

B. LICENSE FEE MANAGEMENT BRANCH (CHECK WHEN MILESTONE 03 IS ENTERED /-√/)

1. FEE CATEGORY AND AMOUNT: 3D $330

2. CORRECT FEE PAID. APPLICATION MAY BE PROCESSED FOR:
AMENDMENT ---√---
RENEWAL ---
LICENSE ---

3. OTHER ---

SIGNED R Brown
DATE 11/7/92