NRC FORM 313
(1-84)
10 CFR 30, 32, 33, 34, 35 and 40

U.S. NUCLEAR REGULATORY COMMISSION
APPROVED BY OMB
3150-0120
Expires: 5-31-87

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.

FEDERAL AGENCIES 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 JERSEY, NEW YORK, PENNSYLVANIA, RHODE ISLAND, OR VERMONT, SEND APPLICATIONS TO:

U.S. NUCLEAR REGULATORY COMMISSION, REGION I
NUCLEAR MATERIAL 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
MATERIAL RADIATION PROTECTION 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
MATERIAL RADIATION PROTECTION 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
- [X] B. AMENDMENT TO LICENSE NUMBER 20-20973-02MA
- [ ] C. RENEWAL OF LICENSE NUMBER _____

2. NAME AND MAILING ADDRESS OF APPLICANT (Include Zip Code)

CIS-US, Inc.
5 De Angelo Drive
Bedford, MA 01730

3. ADDRESS(ES) WHERE LICENSED MATERIAL WILL BE USED OR POSSESSED.

CIS-US, Inc.
5 De Angelo Drive
Bedford, MA 01730

4. NAME OF PERSON TO BE CONTACTED ABOUT THIS APPLICATION

Rita McCullough or Herbert Malamud, Ph.D.

TELEPHONE NUMBER
(617)275-7120 or
(516)326-4381

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 A

8801270554 870814
REG1 LIC30
20-20973-02MA PDR

10. RADIATION SAFETY PROGRAM.

11. WASTE MANA

12. LICENSEE FEES (See 10 CFR 170 and Section 170.31)

FEE CATEGORY 170.31.3.D | AMOUNT ENCLOSED $120.00

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
Herbert Malamud	Herbert Malamud, Ph.D.	Manager, Regulatory Affairs	JUL 07 1987

14. VOLUNTARY ECONOMIC DATA

a. ANNUAL RECEIPTS

- [ ] < $250K
- [ ] $250K – 500K
- [ ] $500K – 750K
- [ ] $750K – 1M
- [ ] $1M – 3.5M
- [ ] $3.5M – 7M
- [ ] $7M – 10M
- [ ] > $10M

b. NUMBER OF EMPLOYEES (Total for entire facility excluding outside contractors)

c. NUMBER OF BEDS

d. WOULD YOU BE WILLING TO FURNISH COST INFORMATION (dollar and/or staff hours) ON THE ECONOMIC IMPACT OF CURRENT NRC REGULATIONS OR ANY FUTURE PROPOSED NRC REGULATIONS THAT MAY AFFECT YOU? (NRC regulations permit it to protect confidential commercial or financial proprietary information furnished to the agency in confidence)

- [ ] YES
- [ ] NO

FOR NRC USE ONLY

TYPE OF FEE	FEE LOG	FEE CATEGORY	COMMENTS	APPROVED BY
AMD	Jul 11	3D	07 JUL 1987	S. Kimberly
AMOUNT RECEIVED	CHECK NUMBER			DATE
$120	005475			7/23/87

PRIVACY ACT STATEMENT ON THE REVERSE

107523

PRIVACY ACT STATEMENT

Pursuant to 5 U.S.C. 552a(e)(3), enacted into law by section 3 of the Privacy Act of 1974 (Public Law 93-579), the following statement is furnished to individuals who supply information to the Nuclear Regulatory Commission on NRC Form 313. This information is maintained in a system of records designated as NRC-3 and described at 40 Federal Register 45334 (October 1, 1975).

1. **AUTHORITY:** Sections 81 and 161(b) of the Atomic Energy Act of 1954, as amended (42 U.S.C. 2111 and 2201(b)).

2. **PRINCIPAL PURPOSE(S):** The information is evaluated by the NRC staff pursuant to the criteria set forth in 10 CFR Parts 30, 32, 33, 34, 35 and 40 to determine whether the application meets the requirements of the Atomic Energy Act of 1954, as amended, and the Commission's regulations, for the issuance of a radioactive material license or amendment thereof.

3. **ROUTINE USES:** The information may be (a) provided to State health departments for their information and use; and (b) provided to Federal, State, and local health officials and other persons in the event of incident or exposure, for their information, investigation, and protection of the public health and safety. The information may also be disclosed to appropriate Federal, State, and local agencies in the event that the information indicates a violation or potential violation of law and in the course of an administrative or judicial proceeding. In addition, this information may be transferred to an appropriate Federal, State, or local agency to the extent relevant and necessary for an NRC decision or to an appropriate Federal agency to the extent relevant and necessary for that agency's decision about you.

4. **WHETHER DISCLOSURE IS MANDATORY OR VOLUNTARY AND EFFECT ON INDIVIDUAL OF NOT PROVIDING INFORMATION:** Disclosure of the requested information is voluntary. If the requested information is not furnished, however, the application for radioactive material license, or amendment thereof, will not be processed. A request that information be held from public inspection must be in accordance with the provisions of 10 CFR 2.790. Withholding from public inspection shall not affect the right, if any, of persons properly and directly concerned need to inspect the document.

5. **SYSTEM MANAGER(S) AND ADDRESS:** U.S. Nuclear Regulatory Commission
Director, Division of Fuel Cycle and Material Safety
Office of Nuclear Material Safety and Safeguards
Washington, D.C. 20555

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555

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Item 5. a. Element and mass number - Not Applicable

b. Chemical and physical forms

AN-PYROTEC is a reagent, meant to be tagged with radioactive Tc-99m by the user. It is not, itself, radioactive. Each vial contains 12.0 mg sodium pyrophosphate and 2.8 to 4.9 mg of stannous tin as a chloride dihydrate. Additional details are given in the package insert.

c. Maximum possession amount - Not Applicable.

Item 6. Technetium Tc-99m Pyrophosphate (AN-PYROTEC), after technetium 99m tagging is used as a bone imaging agent to show altered osteogenesis, a cardiac imaging agent to show areas of myocardial infarction, and a blood pool imaging agent used for gated blood pool imaging and for detection of gastrointestinal bleeding sites.

Item 7. Not Applicable.

Item 8. Not Applicable.

Item 9. Not Applicable.

Item 10.3.1. A copy of the FDA's, NDA approval is attached as Attachment 1.

Item 10.3.2. As per paragraph 35.200, see Attachment 1.

Item 10.3.3. As per 32,72(a) of 10CFR32, we submit the following information:

1. This reagent is intended to be tagged with Technetium-99m from Technetium-99m pertechnetate.

2. The AN-PYROTEC kit is supplied as a set of 5 multi-use vials. Each contains 12.0 mg sodium pyrophosphate and 2.8 to 4.9 mg stannous tin

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(617) 275-7120

as stannous chloride dihydrate. The pH is adjusted to between 5.3 and 5.7 with hydrochloric acid before lyophilization.

3. A sample of the packaging box is included as Attachment 2.

Item 10.3.4 Copies of sample labels and of the package insert are included as Attachment 3.

Item 11 Not Applicable

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

An 1

NDA 19-039

CIS-US, Inc.
1983 Marcus Avenue
Lake Success, New York 11042

JUN 30 1987

Attention: Herbert Malamud, Ph.D.
Manager
Regulatory Affairs

Dear Dr. Malamud:

Reference is made to your new drug application dated May 19, 1983 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for diagnostic radiopharmaceutical AN-PYROTEC (kit for the preparation of technetium Tc 99m pyrophosphate).

We also acknowledge receipt of your additional communications dated January 21, February 28, July 2, October 27, 1986 and April 23, April 27, May 1, and May 21, 1987 amending the application.

We have completed the review of this application including the submitted draft labeling and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted draft labeling. Accordingly, the application is approved, effective as of the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted May 1, 1987 and amended May 21, 1987. 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 available. For administrative purposes this submission should be designated "FPL Supplement" to the approved NDA 19-039. Approval of this supplement 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 the drug product when it is 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,

John F. Palmer

John F. Palmer, M.D.
Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Drug Research and Review
Center for Drugs and Biologics

AN-PYROTEC®

AN-PYROTEC®

AN-PYROTEC®

KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m PYROPHOSPHATE

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

Manufactured for

CIS-US, INC.

5 DeAngelo Drive
Bedford, MA 01730

Distributed by

SYNCOR INTERNATIONAL CORPORATION

20001 Prairie Street
Chatsworth, CA 91311

Sterile Diagnostic Multidose Non-Pyrogenic

CONTENTS: 1 package insert, 10 radiation labels and 5 reaction vials. Each 10mL reaction vial contains 12.0 mg sodium pyrophosphate, 2.8 mg minimum stannous tin as stannous chloride dihydrate and 4.9 mg maximum total tin, as stannous chloride dihydrate; pH is adjusted with HCl prior to lyophilization. Sealed under nitrogen. Contains no bacteriostatic preservative. For intravenous use only after labeling with oxidant-free Technetium Tc 99m or isotonic saline. Do not use if solution is cloudy.

STORE KIT AS PACKAGED AT 15-30°C

Store reconstituted vials at 15-30°C. Use within 6 hours after reconstitution. Refer to Package Insert for recommended adult doses.

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

RM 2A-022
REV. 4/87

Attn

SHIELD LABEL

AN-PYROTEC®

STERILE, NON-PYROGENIC
DIAGNOSTIC, MULTIDOSE
TECHNETIUM Tc 99m PYROPHOSPHATE
FOR INTRAVENOUS USE

Total mCi (KBq) _____ Volume _____

Assay _____ mCi (KBq)/mL as of _____

Each 10 mL reaction vial contains 12.0 mg sodium pyrophosphate, 2.8 mg minimum stannous tin as stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted to 5.3-5.7 with HCl prior to lyophilization. Sealed under nitrogen. Contains no bacteriostatic preservative. For intravenous use only after labeling with oxidant-free Technetium Tc 99m. Do not use if solution is cloudy. Store reconstituted vial at 15-30°C. Use within 6 hours after labeling with Technetium Tc 99m. Refer to Package Insert for recommended adult doses.
(SEE ENCLOSED PACKAGE INSERT)
CAUTION: Federal (U.S.A.) law prohibits dispensing without prescription.

Manufactured in the U.S.A. for
CIS-US, INC., Bedford, MA 01730

4/87

Lot No.

VIAL LABEL

STERILE DIAGNOSTIC MULTIDOSE NON-PYROGENIC

AN-PYROTEC®

KIT FOR THE PREPARATION OF TECHNETIUM Tc 99m PYROPHOSPHATE

Each 10 mL reaction vial contains 12.0 mg sodium pyrophosphate, 2.8 mg minimum stannous tin as stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted to 5.3 to 5.7 with HCl prior to lyophilization. Sealed under nitrogen. Refer to Package Insert for directions for use and the recommended adult doses.

Manufactured in the USA for
CIS-US, INC.
Bedford, MA 01730

4/87

Blood Pool Imaging

The estimated absorbed radiation doses to an average adult patient (70 kg) from an intravenous injection of 740 megabecquerels (20 mCi) of Sodium Pertechnetate Tc 99m Injection, 30 minutes after the intravenous administration of the non-radioactive reconstituted AN-PYROTEC™ are shown in Table 5.

Table 5. Estimated Absorbed Radiation Doses
Blood Pool Imaging[c]

Target Organ	Sodium Pertechnetate Tc 99m 30 min. Post Injection with Pyrophosphate mGy/740 MBq	rads/20 mCi
Total Body	3.2	0.32
Spleen	3.6	0.36
Bladder Wall[d]	24	2.4
Testes	2.4	0.24
Ovaries	4.6	0.46
Blood	10.4	1.04
Red Marrow	4.4	0.44

c Assume 75% of the Sodium Pertechnetate Tc 99m labels red blood cells and that other 25% remains as pertechnetate.

d If 25% excreted with 1 hour T_b Method of calculation: MIRD Dose Estimate Report, No. 8, *J Nucl Med* 17: 74-77, 1976.

HOW SUPPLIED

The AN-PYROTEC™ Kit for the Preparation of Technetium Tc 99m Pyrophosphate is supplied as a set of 5 sterile, non-pyrogenic, white-capped 10 mL vials. Each multidose vial contains 12.0 mg sodium pyrophosphate, 2.8 mg minimum stannous tin as stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted with hydrochloric acid to 5.3-5.7 prior to lyophilization. No bacteriostatic preservative is present. Sealed under nitrogen. Included in each 5-vial kit are one package insert and 10 radiation labels. Store the kit as packaged at 15-30°C. Store the reconstituted vials at 15-30°C.

Directions for Use

Bone and Cardiac Imaging

Technetium Tc 99m Pyrophosphate Injection is prepared from AN-PYROTEC™ by the following aseptic procedure:

1. Waterproof gloves should be worn during the preparation procedure. Remove the white flip-off cap from the AN-PYROTEC™ vial and swab the top of the vial closure with alcohol to sterilize the surface.
2. Complete the radiation label and affix to the vial. Place the vial in an appropriate radiation shield suitably labeled and identified.
3. With a sterile shielded syringe, aseptically obtain 1-10 milliliters of a suitable, oxidant-free, sterile and non-pyrogenic Sodium Pertechnetate Tc 99m Injection containing no more than 3.7 gigabecquerels (100 mCi). Aseptically add the Sodium Pertechnetate Tc 99m Injection to the vial.
4. Swirl the contents of the vial for one minute and let stand for at least 10 minutes.
5. Record date and time of preparation.
6. It is recommended that the radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration.
7. Examine vial contents for particulates and discoloration prior to injection.
8. Withdrawals for administration must be made aseptically using a sterile shielded syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from a vial, the replacement of contents with air should be minimized.
9. Aseptically withdraw material with a sterile lead shielded syringe for use within six (6) hours of preparation. For optimal results, this time should be minimized. The vial contains no bacteriostatic preservative. Store the reconstituted vial at 15-30°C. Discard the vial six (6) hours after reconstitution.
10. The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

Blood Pool Imaging

The non-radioactive AN-PYROTEC™ is prepared by adhering to the following aseptic procedure:

1. Remove the white flip-off cap from the AN-PYROTEC™ vial and swab the top of the vial closure with alcohol to sterilize the surface.
2. Reconstitute the reaction vial with 3 milliliters of sterile, non-pyrogenic, isotonic saline containing no preservatives.
3. Swirl the contents of the vial for one minute and let stand for at least 10 minutes.
4. Record date and time of preparation.
5. Examine vial contents for particulates and discoloration prior to injection.
6. Withdrawals for administration must be made aseptically using a sterile syringe and needle. Since the vials contain nitrogen to prevent oxidation of the complex, the vials should not be vented. If repeated withdrawals are made from a vial, the replacement of contents with air should be minimized.
7. Aseptically withdraw the reconstituted non-radioactive AN-PYROTEC™ with a sterile syringe for use within six (6) hours of preparation. For optimal results, this time should be minimized. The vial contains no bacteriostatic preservative. Store the reconstituted vial at 15-30°C. Discard the vial six (6) hours after reconstitution.
8. A dose of 5-15.4 mg of stannous pyrophosphate may be administered by direct venipuncture 30 minutes prior to the intravenous administration of 555 to 740 megabecquerels (15-20 mCi) of Sodium Pertechnetate Tc 99m Injection. Heparinized catheter systems should not be used.
9. It is recommended that the radiochemical purity of the prepared radiopharmaceutical should be checked prior to patient administration.
10. The patient dose of Sodium Pertechnetate Tc 99m Injection should be measured by a suitable radioactivity calibration system immediately prior to administration.

"This reagent kit is approved by the U.S. Nuclear Regulatory Commission for the 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."

CIS-US, INC., 1983 Marcus Avenue, Lake Success, NY 11042-1016
800-221-7554; in NY State: 516-326-8008

Manufactured in the USA for
CIS-US, INC.
5 DeAngelo Drive
Bedford, MA 01730-2267
617-275-7120

April 1987

Distributed by
SYNCOR INTERNATIONAL CORPORATION
20001 Prairie Street
Chatsworth, CA 91313-2185
818-886-9765
Outside California
800-435-0165

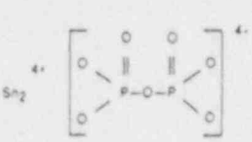
AN-PYROTEC™
Kit for the Preparation of Technetium Tc 99m Pyrophosphate For Diagnostic Use

DESCRIPTION

AN-PYROTEC™ Kit for the Preparation of Technetium Tc 99m Pyrophosphate is a multidose reaction vial which contains the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Pyrophosphate Injection for diagnostic use by intravenous injection.

Each 10 mL vial contains 12.0 mg of sodium pyrophosphate, 2.8 mg minimum stanneous tin as stannous chloride dihydrate and 4.9 mg maximum total tin as stannous chloride dihydrate; pH is adjusted to 5.3-5.7 with hydrochloric acid prior to lyophilization. No bacteriostatic preservative is present. Sealed under nitrogen.

The chemical names are: (1) Diphosphonic acid, distn (2+) salt; (2) Distn (2+) pyrophosphate (4-). The structural formula is



When a solution of sterile, non-pyrogenic, oxidant-free isotonic Sodium Pertechnetate Tc 99m Injection is added to the vial, Technetium Tc 99m Pyrophosphate Injection is formed for intravenous administration.

When a solution of sterile, non-pyrogenic, isotonic saline is added to the vial, it forms a blood pool imaging agent when Sodium Pertechnetate Tc 99m Injection is injected intravenously 30 minutes after the intravenous administration of the non-radioactive reconstituted AN-PYROTEC™. The precise structure of Technetium Tc 99m Pyrophosphate Injection is not known at this time.

Physical Characteristics

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

Table 1. Principal Radiation Emission Data

Radiation	Mean Percent Per Disintegration	Mean Energy (keV)
Gamma-2	89.07	140.5

[1]Kocher DC. Radioactive decay data tables. *DOE/TIC-11026*: 108, 1981.

External Radiation

The specific gamma ray constant for Tc 99m is 0.63 R/hr-millicurie at 1 cm. The first half-value layer is 0.025 cm of lead (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. For example, the use of a 0.26 cm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

Table 2. Radiation Attenuation by Lead Shielding[1]

Shield Thickness (Pb) cm	Coefficient of Attenuation
0.025	0.5
0.086	10^{-1}
0.174	10^{-2}
0.261	10^{-3}
0.349	10^{-4}

[1]Data supplied by Oak Ridge Associated Universities, Radiopharmaceutical Internal Dose Information Center, 1984.

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	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

When injected intravenously, Technetium Tc 99m Pyrophosphate injection has a specific affinity for areas of osteogenesis. It is also concentrated in the injured myocardium, primarily in areas of irreversibly damaged myocardial cells.

One to two hours after intravenous injection of Technetium Tc 99m Pyrophosphate injection, an estimated 40 to 50 percent of the injected dose has been taken up by the skeleton, and approximately 0.01 to 0.02 percent per gram of acutely infarcted myocardium. Within a period of one hour, 10 to 11 percent remains in the vascular system, declining to approximately 2 to 3 percent twenty-four hours post injection. The average urinary excretion was observed to be about 40 percent of the administered dose after 24 hours.

The non-radioactive reconstituted AN-PYROTEC® also has an affinity for red blood cells. When administered 30 minutes prior to the intravenous administration of Sodium Pertechnetate Tc 99m Injection, approximately 76 percent of the injected activity remains in the blood pool providing excellent images of the cardiac chambers.

INDICATIONS AND USAGE

Technetium Tc 99m Pyrophosphate Injection is a bone imaging agent used to demonstrate areas of altered osteogenesis, and a cardiac imaging agent used as an adjunct in the diagnosis of acute myocardial infarction.

AN-PYROTEC® is a blood pool imaging agent which may be used for gated blood pool imaging and for the detection of sites of gastrointestinal bleeding. When reconstituted with sterile non-pyrogenic isotonic saline and administered intravenously 30 minutes prior to the intravenous administration of sodium pertechnetate Tc-99m, approximately 76% of the injected radioactivity remains in the blood pool.

CONTRAINDICATIONS

None known.

WARNINGS

As an adjunct in the diagnosis of confirmed myocardial infarction (ECG and serum enzymes positive), the incidence of false negative images has been found to be 6 percent. False negative images can also occur if made prior to 24 hours in the evolutionary phase of the infarct or after 6 days in the resolution phase. In a limited study involving 22 patients in whom the ECG was positive and serum enzymes questionable or negative, but in whom the final diagnosis of acute myocardial infarction was made, the incidence of false negative images was 23 percent. The incidence of false positive images has been found to be 7 to 9 percent. False positive images have also been reported following coronary by-pass graft surgery, in unstable angina pectoris, old myocardial infarcts and in cardiac contusions.

Preliminary reports indicate impairment of brain scans using Sodium Pertechnetate Tc 99m 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. Alternately, a brain imaging agent such as Technetium Tc 99m Pentetate Injection may be employed.

PRECAUTIONS

General

The lyophilized contents of the AN-PYROTEC® reaction vial are to be administered to the patient only as an intravenous solution (see Procedures for Reconstitution). Any Sodium Pertechnetate Tc 99m solution which contains an oxidizing agent is not suitable for use with AN-PYROTEC®. When reconstituted with Sodium Pertechnetate Tc 99m Injection, AN-PYROTEC® must be used within 6 hours. AN-PYROTEC® may also be reconstituted with sterile, non-pyrogenic isotonic saline containing no preservatives and injected intravenously prior to the administration of Sodium Pertechnetate Tc 99m Injection.

AN-PYROTEC® contains no preservatives.

Vials are sealed under nitrogen; air or oxygen is harmful to the contents of the vials and the vials should not be vented.

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

Shielding should be utilized when preparing Technetium Tc 99m Pyrophosphate Injection.

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

The solution should not be used if cloudy, discolored, or found to contain particulate matter.

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.

No special handling is required for the non-radioactive drug product.

Bone Imaging

Both prior to and following Technetium Tc 99m Pyrophosphate Injection administration, if not contraindicated for the patient's cardiac condition, patients should be encouraged to drink fluids. Patients should void as often as possible after the Technetium Tc 99m Pyrophosphate Injection to minimize background interference and unnecessary radiation exposure from accumulation in the bladder.

Cardiac Imaging

Patient's cardiac condition should be stable before beginning the cardiac imaging procedure.

Interference from chest wall lesions such as breast tumors and healing rib fractures can be minimized by employing the three recommended projections. (See DOSAGE AND ADMINISTRATION). False-positive and false-negative myocardial scans may occur; therefore, the diagnosis of acute myocardial infraction depends on the overall assessment of laboratory and clinical findings.

Blood Pool Imaging

The non-radioactive reconstituted agent should be injected by direct venipuncture. Heparinized catheter systems should be avoided, as interference with red blood cell tagging will result. Cardiac pool imaging should be initiated 15 to 30 minutes after the administration of Sodium Pertechnetate Tc 99m Injection.

The imaging of gastrointestinal bleeding is dependent on such factors as the region of imaging, rate and volume of the bleed, efficacy of the 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 36 hours.

Technetium Tc 99m Pyrophosphate Injection and the non-radioactive reconstituted AN-PYROTEC® should be formulated within six (6) hours prior to clinical use.

Carcinogenesis, Mutagenesis, Impairment of Fertility

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

Pregnancy Category C

Animal reproduction and teratogenicity studies have not been conducted with Technetium Tc 99m Pyrophosphate Injection. It is also not known whether Technetium Tc 99m Pyrophosphate Injection can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Technetium Tc 99m Pyrophosphate 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 Pyrophosphate Injection is excreted in human milk during lactation, therefore, formula feeding should be substituted for breast feeding.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

Some hypersensitivity reactions have been associated with pyrophosphate use.

DOSAGE AND ADMINISTRATION

After preparation with oxidant-free Sodium Pertechnetate Tc 99m Injection, the suggested dose range of Technetium Tc 99m Pyrophosphate Injection in the average ADULT patient (70 kg) is:

Bone Imaging -	185 - 555 megabecquerels (5-15 mCi) (1 - 15.4 milligrams of stannous pyrophosphate)
Cardiac Imaging -	370 - 555 megabecquerels (10-15 mCi) (4 - 7 milligrams of stannous pyrophosphate)

The suggested dose range of the non-radioactive reconstituted AN-PYROTEC® in the average ADULT patient (70 kg) is:

Blood Pool Imaging -	5 - 15.4 milligrams of stannous pyrophosphate [555 - 740 megabecquerels (15-20 mCi) of Pertechnetate Tc 99m Injection]

Bone and Cardiac Imaging

Technetium Tc 99m Pyrophosphate Injection is injected intravenously over a 10 to 20 second period. For optimal results, bone imaging should be done 1 to 6 hours following administration. Cardiac imaging should be done 30 to 90 minutes following administration. The acute myocardial infarct can be visualized from 24 hours to 6 days following onset of symptoms, with maximum localization at 48 to 72 hours. Cardiac imaging should be done with a gamma scintillation camera. It is recommended that images be made of the anterior, left anterior oblique and left lateral projections.

Blood Pool Imaging

AN-PYROTEC® may be reconstituted with sterile, non-pyrogenic isotonic saline containing no preservatives. A dose of 5 to 15.4 milligrams may be administered intravenously 30 minutes prior to the intravenous administration of 555 to 740 megabecquerels (15-20 mCi) Sodium Pertechnetate Tc 99m Injection. The non-radioactive reconstituted AN-PYROTEC® should be injected by direct venipuncture. Heparinized catheter systems should be avoided. Cardiac imaging should be done 10 to 30 minutes following the administration of Sodium Pertechnetate Tc 99m injection utilizing a scintillation camera interfaced to an electrocardiographic gating device.

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

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

Radiation Dosimetry

Bone and Cardiac Imaging

The effective half-life was assumed to be the physical half-life for all calculated values. The estimated radiation absorbed doses to an average ADULT patient (70 kg) from an intravenous injection of a maximum of 555 megabecquerels (15 mCi) of Technetium Tc 99m Pyrophosphate Injection are shown in Table 4.

Table 4. Estimated Absorbed Radiation Doses
Bone and Cardiac Imaging

Target Organ	Technetium Tc 99m Pyrophosphate mGy/555 MBq	rads/15 mCi
Total Body[a]	2.3	0.23
Kidneys	7.1	0.71
Bone Marrow	5.7	0.57
Skeleton[b]	8.1	0.81
Bladder Wall		
2 hour void	14.6	1.46
4.8 hour void	34.5	3.45
Testes		
2 hour void	1.5	0.15
4.8 hour void	2.3	0.23
Ovaries		
2 hour void	1.4	0.14
4.8 hour void	2.3	0.23

a. If patient voids frequently after the radiopharmaceutical is administered, this dose will be reduced.

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

030-29223

BETWEEN: C. James Holloway, Chief
License Fee Management Branch
Office of Resource Management

John E. Glenn, Chief
Nuclear Materials Safety & Safeguards Section B
Division of Radiation Safety and Safeguards

EXPEDITE
03214
5/91

LICENSE FEE TRANSMITTAL

A. REGION I

1. APPLICATION ATTACHED

Applicant/Licensee: CIS-US, Inc.

Application Dated: 7-7-87

Control No.: 107523

License No.: 20-20973-02MA

2. FEE ATTACHED

Amount: ∅

Check No.: ∅

3. COMMENTS

Signed SLJ

Date 7-16-87

B. LICENSE FEE MANAGEMENT BRANCH

1. Fee Category and Amount: 3D $120

2. Correct Fee Paid. Application may be processed for:

Amendment ✓

Renewal

License

EXPEDITE

Signed D. Kimberly

Date 7/23/87

REGION I FORM 213
(MARCH 1987)