AP

NOV 2 8 1978

NDA 18-035

Merck, Sharp & Dohme
Division of Merck & Co., Inc.
Attention: C. Balant, Ph.D.
West Point, Pennsylvania 19488

Gentlemen:

We are pleased to acknowledge the receipt on September 12, 1978, of your communication dated September 8, 1978, enclosing printed labeling pursuant to your new drug application for TechneScan MDP Kit (Technetium Tc 99m Medronate Sodium Kit).

The application was filed on September 12, 1978.

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.

Although we are taking the above action, we request that the following information be submitted, and labels/labeling revisions be made, at the time of the next printing or within six months, whichever is sooner:

1) The revised method for stannous chloride in the September 8, 1978, submission should be sent to both of the FDA validating laboratories.

2) The approvable specifications for methylene diphosphonic acid provided in the March 20, 1978, submission, section 8(d) page 17, (Statistical No 54925) should also be used for the stability study protocol given in item 8n of that submission. Both proton and P31 NMR should be listed.

3) The statement of the quantitative composition of the drug should be revised to reflect the addition of —% more stannous chloride. This will replace the —% overage for stannous chloride now included in the manufacturing process.

4) The quantitative composition of the drug should be revised to state the minimum amount of stannous chloride and the maximum amount of total tin (stannous and stannic) present in the final drug product.

5) The six hour expiration date for the reconstituted drug should appear in bold type print on the carton label.

Please submit one market package of the drug when available.

Sincerely yours,

/S/

Marion J. Finkel, M.D.
Associate Director
for New Drug Evaluation
Bureau of Drugs

Enclosures: Records and Reports Requirements (21 CFR 310.300)
Conditions of Approval of NDA

cc: PHI-DO
Orig. NDA
HFD-616
HFD-150
HFD-150/RJPodliska/10/30/78/ls/10/31/78
R/D init. by: GHDeighton/10/31/78

APPROVAL

/S/ 11-3-78 /S/ 11/8/78 /S/ 11/17/78 /S/ 11/17/78 /S/ 11-13-78 /S/ 11-20-78 /S/ 24 NOV 20 1978

SBA

NOTICE OF APPROVAL
NEW DRUG APPLICATION OR SUPPLEMENT

NDA NUMBER: 18-035

DATE APPROVAL LETTER ISSUED: NOV 2 0 1978

TO: Press Relations Staff (HFI-40)

FROM:
- [X] Bureau of Drugs
- [ ] Bureau of Veterinary Medicine

ATTENTION

Forward original of this form for publication only after approval letter has been issued and the date of approval has been entered above.

TYPE OF APPLICATION
- [X] ORIGINAL NDA
- [ ] SUPPLEMENT TO NDA
- [ ] ABBREVIATED ORIGINAL NDA
- [ ] SUPPLEMENT TO ANDA

CATEGORY
- [X] HUMAN
- [ ] VETERINARY

TRADE NAME *(or other designated name)* AND ESTABLISHED OR NONPROPRIETARY NAME *(if any)* OF DRUG

TechneScan(R) MDP Kit (Technetium Tc 99m Medronate Sodium Kit)

DOSAGE FORM: Solution

HOW DISPENSED
- [X] RX
- [ ] OTC

ACTIVE INGREDIENT(S) *(as declared on label. List by established or nonproprietary name(s) and include amount(s), if amount is declared on label.)*

Non radioactive Kit
Content per vial:
10 mg Medronic Acid
1 mg Stannous chloride
Lyophilized and sealed under nitrogen
User supplies the sodium pertechnetate Tc 99m and labels the drug.

NAME OF APPLICANT *(Include City and State)*

Merck Frosst Laboratories
Kirkland (Montreal) Canada

PRINCIPAL INDICATION OR PHARMACOLOGICAL CATEGORY

Radiodiagnostic

COMPLETE FOR VETERINARY ONLY

ANIMAL SPECIES FOR WHICH APPROVED

COMPLETE FOR SUPPLEMENT ONLY

CHANGE APPROVED TO PROVIDE FOR

cc:
NDA 18-035 Orig.
HFD-150
HFD-1500

FORM PREPARED BY

NAME: Kathleen E. Jongedyk — /S/ 10/16/78 — DATE: October 5, 1978

FORM APPROVED BY

NAME: R.H. Wood, Ph.D. — /S/ 10/17/78 — DATE: October 10, 1978

FORM FD 1642 (2/75) PREVIOUS EDITION MAY BE USED UNTIL SUPPLY IS EXHAUSTED.

Please indicate whether you approve of SBA - NDA 18-035

(S/) July 3, 1978
Chemist - Kathleen E. Jongedyk — Date

for (S/) PhD 11/17/78 — 7/3/78
Supervisory Chemist - Rebecca H. Wood, Ph.D. — Date

(S/) 7/3/76
Pharmacologist - Bergene Kawin, Ph. D. — Date

(S/) 7/3/78
Supervisory Pharmacologist - David J. Richman, Ph.D. — Date

(S/) 7/3/78
Medical Officer - Robert O. Knox, M.D. — Date

(S/) 7/5/78
Group Leader - G. Richard Grove, Ph.D. — Date

(S/) 7/10/78
Division Director - William J. Gyarfas, M.D. — Date

SUMMARY FOR BASIS OF APPROVAL

NDA: 18-035

DRUG DESCRIPTIVE NAME: Technetium Medronate Sodium Kit

APPLICANT: Merck Sharp & Dohme
Division of Merck & Co., Inc.
West Point, Pa. 19488

DRUG CLASSIFICATION: 5 CU

DRUG TRADE NAME:

TECHNESCAN MDP Kit

I. INDICATION FOR USE:

Technetium Tc 99m TECHNESCAN MDP may be used as a bone imaging agent to delineate areas of altered osteogenesis.

II. DOSAGE FORM, ROUTE OF ADMINISTRATION AND RECOMMENDED DOSAGE:

The dosage form is an isotonic saline solution of technetium Tc 99m medronate sodium to be administered intravenously.

The recommended dose for the average adult patient (70 kg) is 15 mCi with a range of 10 to 20 mCI.

Optimal imaging results are obtained within one to four hours after administration.

III. MANUFACTURING AND CONTROLS:

A. Manufacturing and Controls:

The new drug substance is medronic acid stannous chloride.

The commercial product is a sterile, pyrogen-free lyophilized mixture of medronate disodium (sodium methylene diphosphonate) and stannous chloride. This is mixed with sodium pertechnetate Tc99m, supplied by the user, to form a complex of technetium Tc 99m medronate sodium and stannous chloride in the finished dosage form of the drug. The exact chemical structure of the technetium Tc 99m medronate sodium complex is unknown.

The stannous chloride is necessary since the stannous ion, Sn (+2), keeps the technetium Tc 99m in the correct valence state to allow labeling of the methylene diphosphonate.

Sodium hydroxide and hydrochloric acid are added during manufacture as requried, to adjust the pH to the desired range. The synthesis of the medronic acid is described.

The identity, strength, quality, and purity of medronic acid and stannous chloride are established by appropriate quantitative and qualitative assays. All others ingredients must meet U.S.P. XIX 1975 specifications.

The finished dosage form of the drug is assayed to establish identity, strength, quality, and purity. In addition, samples from each drug lot are reconstituted with sodium pertechnetate Tc 99m and assayed for radiochemical purity and for biological distribution.

B. Stability Studies:

Data from adequate stability studies have been submitted to support the proposed expiration date for the "cold" kit and the reconstituted drug.

C. Method Validation:

Food and Drug Administration Laboratories have determined that the methods submitted by the applicant are satisfactory for quality control and regulatory purposes.

D. Labeling:

Labels and labeling meet all the technical requirements and include the necessary radioactivity information and warning statement, and symbol.

Labels and labeling include the proprietary name, the non-proprietary name, the complete list of ingredients and their exact amounts, except hydrochloric acid and sodium hydroxide added to adjust the pH. Also included are the control number the expiration date for the "cold" kit and the reconstituted finished dosage form of the drug, the NDA prescription legend, and applicant and distributor names and addresses.

In addition, there is included, a statement of intended use, "sketal imaging", route of administration,," for intravenous use only after labeling",lypohilized", "contains no bacteriostatic preservative, and store solution at 2-8^{o} c".

The trade name provided does not conflict with the trade name of any other drug.

E. Establishment Inspection:

An establishment inspection report has been received which states that the applicant complies with current good manufacturing practices and the provisions of the NDA.

F. Environmental Impact Analysis Report (EIAR):

The environmental impact analysis report is adequate. A further Environmental Impact Statement (EIS) is unnecessary upon the approval of the NDA.

IV. PHARMACOLOGY:

A. This kit, consisting of 1 mg of disodium methylene diphosphonate and 0.1 mg of stannous chloride, is useful for bone imaging when ^{99m}Tc pertechnetate is added. The behavior of this drug is very similar to that of 1, hydroxy-ethylidine-1, 1-disodium phosphonate and other related phosphate compounds, which are also used for bone scanning. The ^{99m}Tc which is used with this kit has a biological half-life which is considered to be equal to its physical half-life of 6.02 hours.

B. At the very low level at which this drug is used, no signs of acute or systemic toxicity have been observed in mice, rats, or dogs. No compound-related histomorphologic alterations were noted in the tissues that were examined microscopically. No toxic symptoms were observed at a dose ten-fold less than one where minimal toxic or pharmacologic symptoms were observed. No reproduction studies were performed.

C. The maximum recommended radioactivity dose of 20 mCi results in a relatively low range of radiation absorbed doses. For this recommended amount of the drug the abosrbed radiation doses are well within acceptable limits.

D. Chemically this drug is very closely related to dissodium ethylidene diphosphonate, which is listed as a "well-established' radiopharmaceutical agent in the announcement of July 29, 1974, FR 36, No. 212, p. 27542 (Title 21, Section 310.503). Because of this very close similarity, and because its efficacy and safety for bone imaging have been demonstrated, it is recommended that this drug may be approved.

V. MEDICAL:

A. Upon intravenous injection, Techne Scan MDP exhibits a specific affinity for areas of altered osteogenesis. In humans, blood levels fall to 4-10% of the injected dose by two hours post-injection and to 3-5% by three hours. During the first 24 hours following its administration in patients with normal renal function 50-75% of the radioactivity is excreted into the urine and less than 2% of the injected dose remains in the vascular system.

Uptake of the Tc 99m in bone appears to be related to osteogenic activity and to skeletal blood perfusion. The deposition in the skeleton is bilaterally symmetrical, with increased accumulation in the axial structure as compared to the appendicular skeleton. There is increased activity in the distal aspect of long bones as compared to the diaphyses. In pediatric patients, in whom the epiphyseal centers are still open, there is more marked accumulation of the radiopharmaceutical in the distal aspects of long bones than is seen in adults in whom the epiphyseal centers are closed. Localized areas of abnormal accumulation of the radiopharmaceutical may be seen in primary skeletal malignancies, metastatic malignancies to bone, acute or chronic osteomyelitis, arthritides, recent fractures, areas of ectopic calcification, Paget's disease, regional migratory osteoporosis, areas of aseptic necrosis, and in general, any pathological situation involving bone in which there is increased osteogenic activity or localized increased osseous blood perfusion. Since increased osteogenic activity and localized increased osseous blood perfusion are not usually present in chronic bone disease, bone imaging agents, in general, are not effective in detecting such diseases. Localized areas of decreased accumulation of the radiopharmaceutical may be noted in areas of bone which have received localized fields of external radiation or to which blood flow has been interrupted. Technescan MDP has also been noted to accumulate in areas of acute myocardial infarction from one to fourteen days after the pathologic event.

B. Myethylene diphosphonate is similar to other phosphates and to disodium etidronate which appear on the "well-established" list of radiopharmaceutical drug products as published in Section 310.503(f)(1) of 21 CFR. Therefore, it was not required that efficacy be established by clinical studies for this product. Reliance of effectiveness was based on the demonstration of adequate manufacturing and controls to establish the fact that this drug will perform as well as already marketed drugs of a similar nature on the "well-established" list.

C. Labeling is acceptable. The draft package insert is consistent with current Bureau of Drugs requirements of style, format, and content.

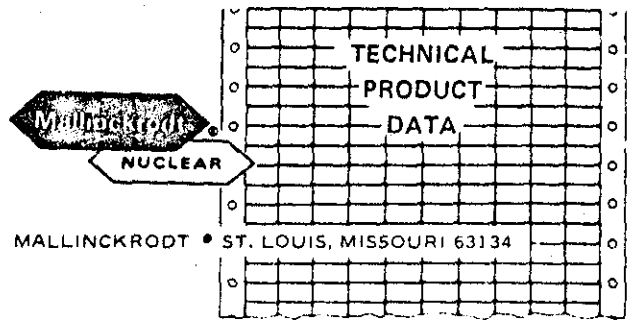
VI. APPROVED PACKAGE INSERT:

A copy of the approved package insert is attached.

LORG
HFD-150
HFD-210

FPL

JANUARY, 1978



TechneScan® MDP KIT

Technetium Tc 99m Medronate Sodium Kit

DIAGNOSTIC

DESCRIPTION

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Medronate Sodium for diagnostic use by intravenous injection.

Each 10 ml reaction vial contains 10 mg medronic acid complexed with 1 mg stannous chloride in lyophilized form under an atmosphere of nitrogen. Sodium hydroxide or hydrochloric acid have been used for pH adjustments. The addition of sodium pertechnetate Tc 99m sterile solution produces a rapid labeling which is essentially quantitative and which remains stable *in vitro* throughout the useful life of the preparation. No bacteriostatic preservative is present.

The precise structure of the reaction vial complex or of its technetium labeled form 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 I.

TABLE I PRINCIPAL RADIATION EMISSION DATA

Radiation	*Mean % Disintegration*	*Mean Energy (keV)*
Gamma-2	88.96	140.5

External Radiation

The specific gamma ray constant for Tc 99m is 0.8 R/mCi-hr at 1 cm. The first half value layer is 0.2 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 2.7 mm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE II RADIATION ATTENUATION BY LEAD SHIELDING

Shield Thickness (Pb) mm	*Coefficient of Attenuation*
0.2	0.5
0.95	10^{-1}
1.8	10^{-2}
2.7	10^{-3}
3.6	10^{-4}
4.5	10^{-5}

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

[1] Martin, M.J., Ed., Nuclear Decay Data for Selected Radionuclides, ORNL Report #5114, p. 24, March, 1976

TABLE III

PHYSICAL DECAY CHART: Tc 99m, half-life 6.02 hours

Hours	*Fraction Remaining*	*Hours*	*Fraction Remaining*
-5	1.778	5	0.562
-4	1.585	6	0.501
-3	1.413	7	0.447
-2	1.259	8	0.398
-1	1.122	9	0.355
0*	1.000	10	0.316
1	0.891	11	0.282
2	0.794	12	0.251
3	0.708	18	0.126
4	0.631	24	0.063

**Calibration time*

CLINICAL PHARMACOLOGY

When injected intravenously, **TECHNETIUM Tc 99m MEDRONATE SODIUM** is rapidly cleared from the blood and accumulates in the skeleton and urine. The skeletal uptake is bilaterally symmetrical being greater in the axial skeleton than in the long bones. Areas of abnormal osteogenesis show altered uptake making it possible to visualize a variety of osseous lesions.

Studies in humans show that, following intravenous injection, about 10% of the injected dose remains in the bloodstream at the end of one hour. This value continues to drop rapidly, being down to about 5% at 2 hours. The resultant disappearance curve appears to be tri-exponential, the two fast components accounting for all but a few percent of the injected activity.

Conversely, there is a rapid deposition in bone and rapid urinary excretion. The rapid blood clearance provides bone to soft-tissue ratios which favor early imaging.

INDICATIONS AND USAGE

TECHNETIUM Tc 99m MEDRONATE SODIUM is a skeletal imaging

agent used to demonstrate areas of altered osteogenesis as seen for example in metastatic bone disease, Paget's disease, arthritic disease and osteomyelitis.

CONTRAINDICATIONS

None known at present.

WARNINGS

This radiopharmaceutical should not be administered to children or to patients who are pregnant or to nursing mothers unless the benefits to be gained outweigh the potential hazards.

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

This class of compound 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., alkalosis).

PRECAUTIONS

General

The finding of an abnormal concentration of radioactivity implies the existence of underlying pathology but further study is required to distinguish benign from malignant lesions.

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

To minimize the radiation dose to the bladder, the patient should be encouraged to void before the examination and as often thereafter as possible for the next 4-6 hours.

The preparation contains no bacteriostatic preservative. Therefore, after labeling with Technetium Tc 99m the solution should be stored at 2-8° C and discarded after 6 hours.

The image quality may be adversely affected by obesity, old age and impaired renal function.

Carcinogenesis

No long term animal studies have been performed to evaluate carcinogenic potential.

Pregnancy

Adequate reproductive studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. There have been no studies in pregnant women. Technetium Tc 99m Medronate Sodium should be used in pregnant women only when clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken while a patient is on the drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

At present adverse reactions have not been reported that are specifically attributable to the use of Technetium Tc 99m Medronate Sodium.

DOSAGE AND ADMINISTRATION

The recommended adult dose is 10 to 20 mCi (200 μCi/kg) by slow intravenous injection over a period of 30 seconds. Optimum scanning time is 1 to 4 hours post-injection.

The patient should be encouraged to drink fluids before and after the examination and to void immediately before imaging is started. This is to minimize the contribution of the bladder content to the image.

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

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.

Radiation Dosimetry

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 20 mCi of Technetium Tc 99m Medronate Sodium are shown in Table IV.

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

TABLE IV RADIATION DOSES

Tissue	*Absorbed Radiation Dose* (rads/20 mCi)
Total Body	0.13
Bone Total	0.70
Red Marrow	0.56
Kidneys	0.80
Liver	0.06
Bladder Wall	
2 hr. void	2.60
4.8 hr. void	6.20
Ovaries	
2 hr. void	0.24
4.8 hr. void	0.34
Testes	
2 hr. void	0.16
4.8 hr. void	0.22

HOW SUPPLIED

TechneScan MDP Kit Technetium Tc 99m Medronate Sodium Kit

Product No. 088

Each kit consists of 5 reaction vials, each vial containing in lyophilized form, sterile and non-pyrogenic:

Medronic Acid	10 mg
Stannous Chloride	1 mg

The pH is adjusted to 6.5 to 7.5 with HCl or NaOH prior to lyophilization. The vials are sealed under an atmosphere of nitrogen.

Labels with radiation warning symbols and directions are supplied with each kit.

DIRECTIONS

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure.

To prepare Technetium Tc 99m Medronate Sodium:

1. Remove the central metal disc from a reaction vial and swab the closure with either an alcohol swab or a suitable bacteriostatic agent.

2. Place the vial in a suitable radiation shield. Obtain from a generator 2-10 ml of sterile, pyrogen-free sodium pertechnetate Tc 99m. The recommended maximum amount of Technetium Tc 99m to be added to a reaction vial is 200 mCi. Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.

3. Add the sodium pertechnetate Tc 99m solution to the reaction vial aseptically.

4. Agitate the shielded vial until the contents are completely dissolved. The solution must be clear and free of particulate matter before proceeding.

5. Assay the product in a suitable calibrator, complete the radioassay information tie-on tag with radiation warning symbol and attach it to the vial.

6. Withdrawals for administration must be made aseptically using a sterile syringe and needle.

7. The finished preparation should be refrigerated at 2 -8° C when not in use and discarded after 6 hours.

"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."

29979

TechneScan® MDP KIT
TECHNETIUM Tc 99m MEDRONATE SODIUM KIT

Manufactured for:

MALLINCKRODT, INC.
St. Louis, Missouri 63134
U.S.A.

By:

MERCK FROSST LABORATORIES
KIRKLAND (MONTREAL), CANADA

MALLINCKRODT, INC. • ST. LOUIS, MO. 63134

Printed in Canada 088 Date Issued 1/78

MED REVIEW

INITIAL MEDICAL REVIEW NDA 18-035

DEC 5 - 1977

Applicant: Merck Sharp & Dohme Laboratories
West Point, Pennsylvania

Date Review Dictated: 11/22/77

Date Review Completed: 11/23/77

180-day deadline: 11/14/77

I. GENERAL INFORMATION:

A. Name of Drug:

1. Generic: Methylene Diphosphonate.

2. Trade: Technetium Tc 99m MDP Kit.

Stannous Methylene Diphosphonate Complex.

3. Chemical:

B. Pharmacologic Category:

Diagnostic radionuclide.

C. Proposed Indications:

Skeletal imaging agent used to demonstrate areas of altered osteogenesis as seen for example in metastatic bone disease, Paget's disease, arthritic disease and osteomyelitis.

D. Dosage Forms and Routes of Administration:

Each kit consists of 5 reaction vials of stannous methylene diphosphonate complex in lyophilized form, sterile and pyrogen-free, each vial containing:

methylene diphosphonic acid (as in a salt)	10 mg
stannous chloride dihydrate (maximum)	1 mg

The vials are sealed under an atmosphere of nitrogen. For intravenous injection.

E. Related Drugs:

Pyrophosphates, polyphosphate and etidronate are also used as bone imaging agents.

II. MANUFACTURING CONTROLS:

Kathleen Jongedyk, 10/11/77

Requests information on reference standard's purity; expiration date, recommended storage conditions; stability data; degradation products in the final drug product; acceptance limits for the in vivo behavior assay; testing schedule for the orthophosphate determination; assays for NDS; filling accuracy test specifications; clarification of reference to NDA —— and labeling.

III. PHARMACOLOGY:

Bergene Kawin, Ph.D., 8/1/77.

Application non-approvable. Requests maximum dose to be given and "its relation to a range of none, or minimum toxicity should be stated;" reconciliation of the several sets of radiation absorbed doses; and explanation of the amount of radiation measured in exiphyses of rabbits.

IV. CLINICAL BACKGROUND:

A. Previous Similar Human Studies and Their Results:

Subramanian et al report on 6 volunteers who are studied with MDP and EHDP. In addition, 400 patients were scanned and imaged with technetium 99m MDP. There were over 200 patients scanned and imaged with EHDP. In more than 40 patients comparative scans were obtained with both agents and compared with several hundred other studies performed with polyphosphate and more than 40 with technetium 99m pyrophosphate. Subramanian concludes that MDP seemed to be the agent of choice for bone imaging.

("Radiopharmaceuticals", the Soc. Nucl. Med. 1975 pp. 319-328).

B. Literature References that are Especially Appropriate:

Jour. Nucl. Med. 16:8, 1975, 744-755. (See paragraph A above).

C. Important Information from Related IND's and NDA's:

Not needed.

V. CLINICAL STUDIES:

A. Controlled Studies:

None have been performed. The investigator's prior experience with similar agents might be considered as an historical control in the phase III studies which are presented."

B. Uncontrolled Studies:

1.

a. A study of the biological fate in humans of technetium 99m methylene diphosphonate as prepared from stannous methylene diphosphonate complex has been made by 3 investigators:

(1) Leonard Freeman, M.D.

(2) N. David Charkes, M.D.

(3) James Quinn, M.D.

The data obtained in a total of 15 patients confirmed that the biological behavior of technetium 99m MDP prepared from kit material conformed to that as expected for this class of compound and in particular to the published results of Subramanian et al (Jour. Nucl. Med. 16:744-755, 1975).

b. The kinetics of technetium 99m MDP and technetium 99m EHDP in humans was compared in a non-Merck, non-IND study by Leonard Rosenthall, M.D. at the Montreal General Hospital, the subject kit preparation was compared with the osteroscan kit (EHDP) by _____ in 11 volunteers and in 20 patient. Both radiopharmaceuticals were tested in each individual. Technetium 99m MDP is claimed to have shown significant superiority in most of the parameters measured but both radiopharmaceuticals disclosed same lesions with approximately equal relief.

2. Phase III Clinical Studies:

Phase III clinical studies were carried out to evaluate technetium 99m MDP as a skeletal imaging agent when prepared using stannous methylene diphosphante (Sn-MDP)

complex. 8 studies were done, 3 in the United States under IND —— and 5 in Canada, not under this IND. All the studies in Canada and the United States were open label studies performed on random patients referred for a bone imaging procedure which is clinically indicated. A total of 623 patients was examined and 625 procedures from a total of 225 preparations:-

Study #	Investigator	Patients	Preparations
2	Freeman	76	47
3	Charke	92	40
6	Quinn	54	23
		222	110
Canadian Studies:			
1	Rosenthall	112	19
2	Farrer	110	33
3	Greyson	74	23
4	Gilday	50	20
5	Chenoweth	55	20
		401	115
Grand Total		623	225

Each examination is performed by single IV injection of MDP at variable times post-preparation. Most adults received a dose of 10-20 millicuries contained in a variable weight and volume of material. Images were obtained using the dual probe, whole body scanner and/or a gamma camera from 1 to 7 hours post-injection.

Results:

Good to excellent quality images were obtained in 550 out of 625 procedures.

Safety: No adverse reactions were reported.

VI. ACCOUNTING FOR INVESTIGATORS:

All investigators accounted for.

VII. LABELING AND REVIEW:

Labeling is medically satisfactory.

VIII. OVER-ALL EVALUATION CONCLUSIONS:

1. The use of technetium 99m-labeled phosphate and phosphonate compounds in place of the ionic radionuclides of strontium and fluorine for bone scintigraphy in recent years has been a major advance. The absorbed radiation dose has been reduced and the result of increase in photon detection efficiency derived from a more favorable decay charateristics of technetium 99m has led to an increased senstivity and resolution in imaging of oseous lesions and thus to an increased diagnostic efficacy. The labeling of polyphosphate with technetium 99m was rapidly followed by the introduction of the pyrophosphate and more recently the diphosphonate. Studies at the Upstate Medical Center, Syracuse, New York indicated that methylene diphosphonate had enhanced biological properties for the scintigraphy of oseous structures. A more rapid blood clearance in animals and humans was noted. This creates a more favorable bone to soft tissue ratio of radioactivity sooner than is possible with the known agents. Images could thus be obtained which showed greater anatomical detail and enhanced the ability to detect the focal regions of the increased uptake of tracer by providing better contrast between pathological and normal areas of bone. The interval between administration and the imaging procedure may thus be shortened and would appear to be the chief advantage. These agents are not specific for malignancies since a variety of benign lesions may also show the same ability to concentrate at the tracer. Bone scintigraphy has been most useful in the detection of Roentgen occult lesions, mainly the assessment of metastatic malignancies.

ographically

2. Since we consider methylene diphosphonate a "well-established" drug, it was deemed unnecessary to have original clinical data to prove safety and efficacy.

IX. RECOMMENDATIONS:

NDA is recommended for approval as far as the medical aspects are concerned.

/S/ DEC 5 1977

Robert O. Knox, M.D.

NDA 18-035 Orig.
HFD-180
HFD-150
HFD-150:ROKnox:mal:11/29/77
ROKnox:11/23/77

12/5/77

12/5/77

CHEM REVIEW

DIVISION OF ONCOLOGY AND RADIOPHARMACEUTICAL DRUG PRODUCTS

OCT 11 1977

Chemist's Review #1

Date Completed: September 28, 1977

A. 1. NDA: 18-035

Applicant: Merck Sharp & Dohme
Research Laboratories
Division of Merck and Company
West Point, Pennsylvania 19486

2. Product Name:

Non-proprietary: Technetium Tc 99m Methylene Diphosphonate Kit

3. Dosage Form and Route of Administration:

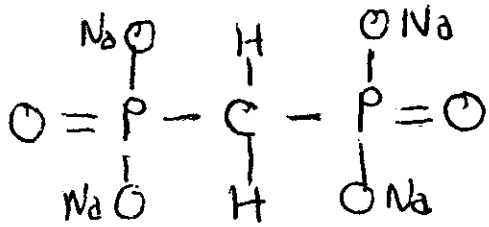
Solution/Intravenous, Rx.

4. Pharmacological Category and/or Principal Indication:

Radiodiagnostic

5. Structural Formula and Chemical Name:

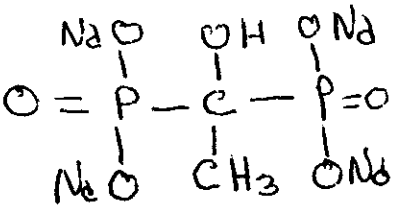
Precise structure of the stannous methylene diphosphonate complex or its technetium labeled form is unknown.



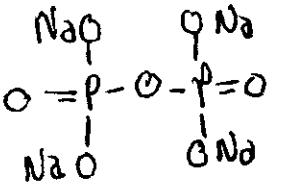
Methylene Diphosphonate

RELATED COMPOUNDS

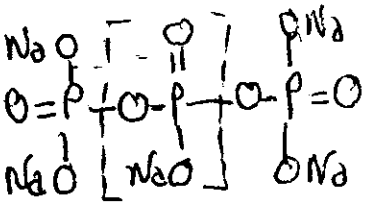
Ethane-1-Hydroxy-1, --Diphosphonate (EHDP)



Pyrophosphate



Polyphosphate



B. 1. Initial Submission:

May 13, 1977

3. Supporting IND, NDA, MF, and Letters of Authorization:

DMF —— -Merck & Company for manufacturing procedures at the Merck Frosst Lab., Kirkland (Montreal) Canada.

NDA —— - Additional description of manufacturing facilities and procedures.

DMF —— - ———————————————— for the manufacturing processes and specifications for methylene diphosphonic acid.

A letter dated September 5, 1975 from ———— to the FDA authroizing reference to their DMF —— in support of this NDA 18-035.

IND —— - The same drug if the same applicant/sponsor.

NDA 17-972 - NEN-MDP Stannous Methylene Diphosphonate Agent.

C. Remarks:

Method validation requested 9/7/77.

EIR requested 9/2/77

NDA is deficient. See E-5, 11, 13, and 15.

D. Conclusions and/or Recommendations:

Inform applicant of the additional information needed as requested in Section C.

S

Kathleen E. Jongedyk

NDA 18-035 Orig.
HFD-102/Kumkumian
HFD-150
HFD-150:KEJongedyk:mal:10/3/77
RHWood:9/29/77 10/5/77

10/7/77

Redacted 13

pages of trade

secret and/or

confidential

commercial

information

Chemist portion of the letter to the applicant:

1. It is noted that the NDA provides for the bulk methylene diphosphonic acid to serve as the reference standard for the drug's assays. What information is available to determine the reference standard's purity?

2. Please provide an expiration date for the new drug substance, methylene diphosphonic acid, and any recommended storage conditions based on data from adequate stability studies.

3. Information should be submitted to show the new drug substance and the final drug product's stability when exposed to visible and ultraviolet light of the approximate intensity of 1000 foot candles.

4. Please identify and quantify by-products derived from the synthesis of methylene diphosphonic acid and any degradation products that might be present in the final drug product.

5. The in vivo behavior assay would better describe the drug action if additional acceptance limits included specifications for the percentage of total radioactivity in the G.I. tract and bone (such as a long bone free of extraneous tissue). In addition the acceptance limits should include a maximum percentage of radioactivity allowed at the site of injection, the tail.

6. Please submit the testing schedule for the orthophosphate determination on the final product.

7. Attachment #2 on page II-00047 of volume 1.3 does not include all assays for the new drug substance listed on the NDA pages II-00005--II-00009; for example, melting point, solubility in and spectra data for proton and phosphorus 31.

   Please provide information as to whether the deleted assays are performed on the methylene diphosphonic acid on a per lot basis and whether they meet the acceptance specifications. It is desirable to include such assays to identify impuirities.

8. Please reconcile the filling accuracy test specifications for the drug with the batch formula statement that 2 ml of the bulk drug solution containing 10 mg MDP and one mg stannous chloride dihydrate is dispensed into each vial.

10. Please identify the New Drug Application referenced in this NDA as NDA

DORDP
1# Chemist Review
NDA 18-935

Chemist portion of the letter to the applicant NDA 19-936 continued 2

10. The name of the kit should read as follows:

Technetium Tc 99m medronate sodium*kit

USAN designation for sodium methylene phosphonate ,MDP

The carton label should include the following additional information:

. The word, diagnostic.
. The expiration date for the labeled drug.
. The statement, "See the enclosed product monograph".
. When the name of the isotope is used, use the USP designation Technetium Tc 99m.
. "For intravenous use after labeling with technetium Tc 9
in accordance with directions supplied". Add the latte
phrase " in accordance with directions supplied".

The container label should include the following additional information:

.The pH statement to read-"pH is adjusted to 6.5=7.5".
.The expiration date for the labeled drug.

All labels and labeling should use the official USAN designations for the drug and the drug's components.

All labels and labeling should carry the expiration date for the labeled drug.

OCT 18 1978

Division of Oncology and Radiopharmaceutical Drug Products

Chemist's Review # 3

October 6, 1978

A. 1. NDA: 18-035

Applicant: Laboratories Merck Frosst Laboratories
A Division of Merck Sharp & Dohme
Address: Kirland (Montreal), Canada

2. Product Name:

Proprietary:
TechneScan MDP Kit

Non-proprietary: Technetium Tc 99m Medronate Sodium Kit

3. Dosage Form: Solution/Intravenous Rx

4. Pharmacological Category: Radiodiagnostic

B. 1. Initial Submission: May 13, 1977.

2. Amendments: September 8, 1978 - Labels and labeling (FP) and manufacturing and control information.

C. REMARKS: Additional information should be requested as outlined in E-11, 13, and 15.

D. Conclusions: The NDA is approved upon the agreement to submit the information and revise the labels and labeling at the next printing or within six months, whichever occurs first, as outlined in section C.

S

Kathleen E. Jongedyk
Chemist

cc:
NDA: 18-035 Orig.
HFD-150
HFD-150/KEJongedyk:10/6/78
R/D Endorsed by RHWood:10/10/78
F/T by deg:10/12/78

10/17/78

11. Laboratory Controls: FDA requested assurance that the frequency of assaying and sampling procedure were adequate to give assay results representative of the entire drug lot.

Lot sizes will vary between — to — vials. — vials are taken for assays.

All capped drug vials are visually inspected for defects and uniformity of the —— plugs.

Solubility and pH determinations are revised to state that the drug vial will be reconstituted with saline.

Stannous chloride assay revised (September 8, 1978) New Method will provide an assay with a sharper more readily detected end point. This assay will now be performed on 3 individual drug vial samples.

. Alternate Assay for stannous chloride- : method remains the same.

13. Stability: A proposed —— expiration date for the new drug substance is made.

This is based on — months stability data obtained from —— (MDP) and from the stability data obtained from the —— studies proposed in the March 20, 1978 submission.

Although Merck will use only MDP produced at their Merck Frosst Laboratories, it is believed that —— MDP stability data is applicable for the —— expiration date. Since the March 20, 1978 submission it is possible that applicant has 6 month stability data on their own MDP, the —— would therefore represent only 6 months projection.

Stability studies immediate drug container and closurer.

Long term [redacted] studies 40 ml bottles-
[redacted] is supplied by [redacted]
[redacted] (# [redacted]).
Capped lids, [redacted] lid is supplied by
[redacted] (# [redacted]
(Specifications provided)

Light studies
Vial, 10 ml, type I Glass - [redacted]

Closure - [redacted]

The final drug products immediate container and closure is identical to those used on the light studies.

Specifications for the MDP in the stability studies and for the drug manufacturer should be the revised March 16, 1978 (See the March 20, 1978, section 8(d) page 17 and section 8n) with the NMR correction.

15. Labeling: Request labels and labeling to be revised to show a [redacted]% increase in stannous chloride instead of allowing a [redacted]% average during the manufacturing process.

The "Description" section does not state the pH specification as typically appears in other package inserts.

JANUARY, 1978

TECHNICAL PRODUCT DATA

Mallinckrodt NUCLEAR

MALLINCKRODT • ST. LOUIS, MISSOURI 63134

TechneScan® MDP KIT

Technetium Tc 99m Medronate Sodium Kit

DIAGNOSTIC

DESCRIPTION

The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Medronate Sodium for diagnostic use by intravenous injection.

Each 10 ml reaction vial contains 10 mg medronic acid complexed with 1 mg stannous chloride in lyophilized form under an atmosphere of nitrogen. Sodium hydroxide or hydrochloric acid have been used for pH adjustments. The addition of sodium pertechnetate Tc 99m sterile solution produces a rapid labeling which is essentially quantitative and which remains stable *in vitro* throughout the useful life of the preparation. No bacteriostatic preservative is present.

The precise structure of the reaction vial complex or of its technetium labeled form 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 I.

TABLE I PRINCIPAL RADIATION EMISSION DATA

Radiation	*Mean % Disintegration*	*Mean Energy (keV)*
Gamma-2	88.96	140.5

External Radiation

The specific gamma ray constant for Tc 99m is 0.8 R/mCi-hr at 1 cm. The first half value layer is 0.2 mm of Pb. To facilitate control of the radiation exposure from millicurie amounts of this radionuclide, the use of a 2.7 mm thickness of Pb will attenuate the radiation emitted by a factor of about 1,000.

TABLE II RADIATION ATTENUATION BY LEAD SHIELDING

Shield Thickness (Pb) mm	*Coefficient of Attenuation*
0.2	0.5
0.95	10^{-1}
1.8	10^{-2}
2.7	10^{-3}
3.6	10^{-4}
4.5	10^{-5}

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

[1] Martin, M.J., Ed., Nuclear Decay Data for Selected Radionuclides, ORNL Report #5114, p. 24, March, 1976

TABLE III

PHYSICAL DECAY CHART: Tc 99m, half-life 6.02 hours

Hours	*Fraction Remaining*	*Hours*	*Fraction Remaining*
-5	1.778	5	0.562
-4	1.585	6	0.501
-3	1.413	7	0.447
-2	1.259	8	0.398
-1	1.122	9	0.355
0*	1.000	10	0.316
1	0.891	11	0.282
2	0.794	12	0.251
3	0.708	18	0.126
4	0.631	24	0.063

**Calibration time*

CLINICAL PHARMACOLOGY

When injected intravenously, **TECHNETIUM Tc 99m MEDRONATE SODIUM** is rapidly cleared from the blood and accumulates in the skeleton and urine. The skeletal uptake is bilaterally symmetrical being greater in the axial skeleton than in the long bones. Areas of abnormal osteogenesis show altered uptake making it possible to visualize a variety of osseous lesions.

Studies in humans show that, following intravenous injection, about 10% of the injected dose remains in the bloodstream at the end of one hour. This value continues to drop rapidly, being down to about 5% at 2 hours. The resultant disappearance curve appears to be tri-exponential, the two fast components accounting for all but a few percent of the injected activity.

Conversely, there is a rapid deposition in bone and rapid urinary excretion. The rapid blood clearance provides bone to soft-tissue ratios which favor early imaging.

INDICATIONS AND USAGE

TECHNETIUM Tc 99m MEDRONATE SODIUM is a skeletal imaging

agent used to demonstrate areas of altered osteogenesis as seen for example in metastatic bone disease, Paget's disease, arthritic disease and osteomyelitis.

CONTRAINDICATIONS

None known at present.

WARNINGS

This radiopharmaceutical should not be administered to children or to patients who are pregnant or to nursing mothers unless the benefits to be gained outweigh the potential hazards.

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

This class of compound 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., alkalosis).

PRECAUTIONS

General

The finding of an abnormal concentration of radioactivity implies the existence of underlying pathology but further study is required to distinguish benign from malignant lesions.

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

To minimize the radiation dose to the bladder, the patient should be encouraged to void before the examination and as often thereafter as possible for the next 4-6 hours.

The preparation contains no bacteriostatic preservative. Therefore, after labeling with Technetium Tc 99m the solution should be stored at 2-8° C and discarded after 6 hours.

The image quality may be adversely affected by obesity, old age and impaired renal function.

Carcinogenesis

No long term animal studies have been performed to evaluate carcinogenic potential.

Pregnancy

Adequate reproductive studies have not been performed in animals to determine whether this drug affects fertility in males or females, has teratogenic potential, or has other adverse effects on the fetus. There have been no studies in pregnant women. Technetium Tc 99m Medronate Sodium should be used in pregnant women only when clearly needed.

Nursing Mothers

It is not known whether this drug is excreted in human milk. As a general rule nursing should not be undertaken while a patient is on the drug since many drugs are excreted in human milk.

Pediatric Use

Safety and effectiveness in children have not been established.

ADVERSE REACTIONS

At present adverse reactions have not been reported that are specifically attributable to the use of Technetium Tc 99m Medronate Sodium.

DOSAGE AND ADMINISTRATION

The recommended adult dose is 10 to 20 mCi (200 μCi/kg) by slow intravenous injection over a period of 30 seconds. Optimum scanning time is 1 to 4 hours post-injection.

The patient should be encouraged to drink fluids before and after the examination and to void immediately before imaging is started. This is to minimize the contribution of the bladder content to the image.

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

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.

Radiation Dosimetry

The estimated absorbed radiation doses[1] to an average patient (70 kg) from an intravenous injection of a maximum dose of 20 mCi of Technetium Tc 99m Medronate Sodium are shown in Table IV.

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

TABLE IV RADIATION DOSES

Tissue	*Absorbed Radiation Dose* (rads/20 mCi)
Total Body	0.13
Bone Total	0.70
Red Marrow	0.56
Kidneys	0.80
Liver	0.06
Bladder Wall	
2 hr. void	2.60
4.8 hr. void	6.20
Ovaries	
2 hr. void	0.24
4.8 hr. void	0.34
Testes	
2 hr. void	0.16
4.8 hr. void	0.22

HOW SUPPLIED

TechneScan MDP Kit Technetium Tc 99m Medronate Sodium Kit

Product No. 088

Each kit consists of 5 reaction vials, each vial containing in lyophilized form, sterile and non-pyrogenic:

Medronic Acid	10 mg
Stannous Chloride	1 mg

The pH is adjusted to 6.5 to 7.5 with HCl or NaOH prior to lyophilization. The vials are sealed under an atmosphere of nitrogen.

Labels with radiation warning symbols and directions are supplied with each kit.

DIRECTIONS

NOTE: Use aseptic procedures throughout and take precautions to minimize radiation exposure.

To prepare Technetium Tc 99m Medronate Sodium:

1. Remove the central metal disc from a reaction vial and swab the closure with either an alcohol swab or a suitable bacteriostatic agent.

2. Place the vial in a suitable radiation shield. Obtain from a generator 2-10 ml of sterile, pyrogen-free sodium pertechnetate Tc 99m. The recommended maximum amount of Technetium Tc 99m to be added to a reaction vial is 200 mCi. Sodium pertechnetate Tc 99m solutions containing an oxidizing agent are not suitable for use.

3. Add the sodium pertechnetate Tc 99m solution to the reaction vial aseptically.

4. Agitate the shielded vial until the contents are completely dissolved. The solution must be clear and free of particulate matter before proceeding.

5. Assay the product in a suitable calibrator, complete the radioassay information tie-on tag with radiation warning symbol and attach it to the vial.

6. Withdrawals for administration must be made aseptically using a sterile syringe and needle.

7. The finished preparation should be refrigerated at 2 -8° C when not in use and discarded after 6 hours.

"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."

29979

TechneScan® MDP KIT
TECHNETIUM Tc 99m MEDRONATE SODIUM KIT

Manufactured for:

MALLINCKRODT, INC.
St. Louis, Missouri 63134
U.S.A.

By:

MERCK FROSST LABORATORIES
KIRKLAND (MONTREAL), CANADA

Mallinckrodt
NUCLEAR

MALLINCKRODT, INC. • ST. LOUIS, MO. 63134

Printed In Canada 088 Date Issued 1/78

Recommended Adult Dose: 10 to 20 millicuries
(see enclosed package insert)

KIT CONTAINS: 5 sterile reaction vials each containing sterile and non-pyrogenic 10 mg Medronic Acid and 1 mg Stannous Chloride. The pH is adjusted to 6.5 to 7.5 with HCl or NaOH prior to lyophilization. Sealed under nitrogen.
5 radioassay information string tags with radiation warning.
1 package insert.

CONTAINS NO BACTERIOSTATIC PRESERVATIVE

No. 088 1067

TechneScan® MDP Kit

Diagnostic—For skeletal imaging

Mallinckrodt NUCLEAR

Manufactured For: **Mallinckrodt, Inc.** St. Louis, Mo. 63134
By: **Merck Frosst** Laboratories Kirkland (Montreal) Canada

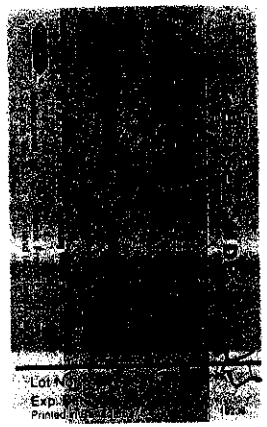
K.J

APPROVED NOV. 2 6 1978

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

FOR INTRAVENOUS USE AFTER LABELING WITH OXIDANT-FREE TECHNETIUM Tc 99m.

In accordance with directions supplied, after labeling with Technetium Tc 99m, store solution at 2°-8°C and use within 6 hours.



Labeling: Orig working copy.
ND. No: 18-035 Rc'd. 9/12/78
Reviewed by: Kathleen E. Engebretsen

Labeling: Orig. Worse Rec'd. 9/12/78

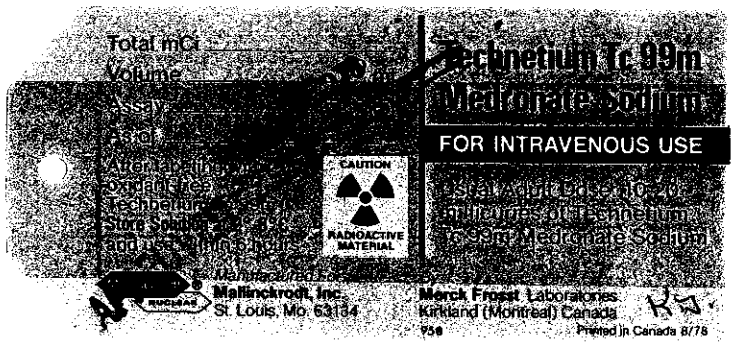
NDA No: 18-035

Reviewed by:

Labeling: Rec'd.

NDA No:

Reviewed by: Kathleen E. Donnelly September 21, 1978



PHARM

REV

August 23, 1977 AUG 1 1977

INITIAL PHARMACOLOGIST REVIEW OF NDA 18-035

NDA: 18-035

NAME OF APPLICANT: Merck Sharp & Dohme
West Point, PA 19486

DATE OF APPLICATION: May 13, 1977

NAME OF DRUG: Technetium Tc 99m Methylene Diphosphonate Kit

CATEGORY: Bone imaging agent

COMPOSITION: Each 10 ml vial contains methylene diphosphonic acid, 10 mg, and stannous chloride dihydrate, 1 mg. From 2 to 10 ml of pertechnetate solution are added to the kit when it is used.

RELATED INDs: [redacted]

RELATED NDAs: None

PRECLINICAL STUDIES: The concentration of the drug in bones of rabbits 2 hrs. after injection was singificantly greater than when polyphosphates or pyrophosphates were used but the blood concentrations of the drug were less than these compounds. About 54% was present in skeleton. Liver contained 0.7%, and kidney and muscle each contained 1.1%. In mice after 24 hrs. about 44% was in skeleton, and 61% was excreted in urine. In rabbits it was reported that up to 233% of the dose was deposited in bone epiphysis. It is reported that the LD_{50} of the drug in mice and rabbits is 45 to 55 mg/kg. In mice an intravenous injection of about 100 mg/kg induced severe clonic convulsions. No mortalities and no gross pathological changes were discovered over a 14-day observation period. There were no signs of intoxication at 40 mg/kg, and gross necroscopy was negative. Similar results were obtained in the rat and beagle dog at a dose of 20 mg/kg.

DOSIMETRY: Radiation absorbed doses are calculated for bone, bone marrow, bladder, kidneys, ovaries, testes, and total body to be 0.48, 0.26, 0.56, 0.32, 0.16, 0.16, and 0.11 rads/15 mCi respectively. Other values that differ from these are also calculated in two other sections of the application.

COMMENT AND EVALUATION: The amount of the drug that will be administered is not stated exactly. The toxicity data does not permit the proposed dose of the drug to be ascertained, and the range of safe use of the drug is not demonstrated. The amount of the maximum recommended dose is stated to be 20 mCi, but radiation doses are calculated for a 15 mCi maximum. Radiation doses are calculated twice, in addition. However, the dosimetry stated for this drug in the sample package insert is displayed for 20 mCi but the basic dose/mCi differs from the others calculated in magnitude and organ type. The metabolic behavior of this drug is very similar to that of ethylene diphosphonate radiopharmaceuticals. Considering this, and the inclusion of the latter drug on the "well-established" list, we do not consider it necessary to recommend the performance of 14-day subacute studies with the methylene diphosphonate drug to demonstrate its safety and efficacy.

RECOMMENDATIONS: This application is nonapprovable. To facilitate evaluation it is recommended that the value of the maximum amount of the drug to be administered per dose should be made clear. Its relation to a range of none, or minimum toxicity should be stated. The lack of agreement between the several sets of radiation absorbed doses calculated in this application, and the values contained in the sample package insert should be reconciled, and adjusted to reflect the maximum recommended amount of radioactivity that will be administered. Please explain the tabulated finding that up to more than twice the value of the full injected dose was measured in bone epiphyses of rabbits.

/S/

Bergene Kawin, Ph.D.

cc:
ORIG NDA 18-035
HFD-180
HFD-150
HFD-150/BKawin/8/23/77
yy/T/F: 9/1/77
R/D endorsed: DJRichman

ADMIN

MEMORANDUM OF MEETING

January 19, 1978

NDA 18-035
Drug: Technetium Tc 99m Medronate Sodium Kit
Applicant - Merck Sharp & Dohme, Merck Frosst Lab.

Participants: Merck-Frosst

Dr. Charles P. Balant	Reg. Affairs MSDRL
Dr. T.W. Tusing	Medical Director, Mallinckrodt
Dr. Kenneth M. Given	Reg. Affairs MSDRL
Erwin Frank	Director Quality Control, Merck Frosst
Gearld Kantorow	Regulatory Affairs
Dr. Richard F. Randall	Director, Clinical Research, Radiopharm. MFL
Dr. L.M. Thompson	Technical Manager, Radiopharmaceutical, MFL

and

Food and Drug Administration

G. Richard Grove, Ph.D.,	- Group Leader of the Radiopharmaceutical Drug Products
Rebecca H. Wood, Ph.D.	Supervisory Chemist, HFD-150
Kathleen E. Jongedyk	- Chemist, HFD-150
Bergene Kawin, Ph.D.	- Pharmacologist, HFD-150

Subject: Deficiencies in NDA 18-035

Dr. Thompson opened the discussion of the deficiencies in the manufacturing and control information by offering to distribute a booklet containing the following information on the reference standard for the NDS.

Evaluation of elemental analysis data, I.R. curves, proton and P^3 NMR curves, heavy metals analysis, and other identification tests.

The reference standard for the NDS is synthesized and tested by Merck and then used for all manufacturing and Q.C. work for the drug.

The NDS for manufacturing the drug is presently purchased from [redacted]

Dr. Wood stated that the Drug Master File of [redacted] for the NDS was deficient in establishing purity of the starting materials used in synthesis, of the intermediates, and of the NDS. The methodology for testing the NDS was inadequate.

There was a discussion as to the adequacy of the assay for methylene diphosphonic acid. This assay determines total phosphorous and is not specific for this compound. All phosphorous containing materials would be included in this assay value.

Dr. Thompson agreed that further work was necessary to completely characterize the methylene phosphonic acid to determine possible impurities and degredation products.

Information sheets were provided by Dr. Thompson containing the protocols or work sheets for the proposed stability studies on the NDS and the final drug product.

Dr. Grove stated that such hand outs were desirable for the discussion at this meeting but for an accurate and complete review these materials should be submitted to the NDA.
After a complete review of these submissions comments would be made.

An explanation for the filling weight exceeding the [redacted] mg per vial after lyophilization was made.

Mrs. Jongedyk and Dr. Thompson discussed the elemental analysis, proton and P31 NMR analysis of the drug. It was agreed that the elemental analysis would not rule out [redacted] impurities but over all would provide a good evaluation of total purity. The proton NMR could identify and quantity the [redacted] impurities. The P31 NMR could identify and quantity the [redacted] impurities.

determination as an assay to ascertain purity was discussed. Dr. Wood said this could not be a good criterium for purity depending upon the impurities. was a topic. It was agreed that while a good technique it required finding the ideal conditions. Even then as Dr. Thompson stated the detection of minor impurities could be lost in the major component.

The applicant agreed to establish the purity of the new drug substance and the final drug product.

A work sheet was submitted by Dr. Thompson providing information of the final drugs quality control sampling procedures; for example, the number of total vials used for quality control tests, the number of vials and samples used per test, the frequency of testing.

Labels and labeling were discussed. Bergene Kawin led the discussion on the dosimetry information. dosimetry data will be used. The package insert will closely follow the format and content of New England Nuclear recently approved, MDP drug. The words and " ' will be deleted from the headings of the labels.

/S/

Kathleen E. Jongedyk

cc:
NDA 18-035 Orig.
HFD-150
HFD-150/KEJongedyk:1/19/78
R/D Endorsed by RHWood:1/27/78
GRGrove:1/27/78
Final typed by deg:2/16/78

RANDUM

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
Winchester Engineering and Analytical Center
109 Holton Street, Winchester, Mass. 01890

DATE: December 13, 1977

eonard A. Ford
cting Chief, Instrumental Applications Research Branch,
DC, BD (HFD-420)

Received K. Jongedyk Chemistry

cting Director, Analytical Branch, WEAC (HFR-1390)

lethod Validation - NDA 18-035 Methylene Disphosphonate Iit
lerck, Sharp & Dohme

ubject NDA 18-035 as received from K. Jongedyk, Reviewing Chemist, has een reviewed and evaluated. The NDA methods as presented are unsuitable or regulatory purposes. Specific comments follow:

ssay for Stannous Chloride Dihydrate

h.. method as written (11-00028-29) is unsuitable since the values obtained ere found to be [redacted] and [redacted] % of label as performed by two separate analysts. he [redacted] method (alternate assay) was suitable.

[redacted]

ssay for Methylene Disphosphonic Acid

The results for this method gave [redacted]% and [redacted]% (as compared with the manufacturer's) for two separate determinations. The analysis of the raw material (MDPA) showed [redacted] % purity even though the wavelength used was [redacted] mn. These former values are [redacted]% and [redacted]% of the minimum required by the specifications for the finished product.

pH Determination

The method calls for reconstitution using [redacted] Since the product is actually reconstituted using saline when dispensed, it would seem only appropriate that it be used rather than the [redacted]

Biodistribution

There is no specification or test for distribution in the bone. Since this is a bone-seeking agent a test and specification for this must be included. The present test is inadequate since it doesn't address itself to this matter.

Radiochemical Purity Test

This test is adequate and the sample met the specifications.

Worksheets attached.

/S/
Edmond J. Baratta

cc:
H. P. Eiduson, Director, FSB, EDRO (HFO-130)
K. Jongedyk, Reviewing Chemist, DORDP, BD (HFD-150) ✓
Director, WEAC (HFR-1300)

ORIG NEW CORRES

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CHARLES P. BALANT, Ph.D.
DIRECTOR
REGULATORY AFFAIRS

October 24, 1977

William J. Gyarfas, M.D., Director
Division of Oncology & Radiopharmaceutical
Drug Products
Bureau of Drugs HFD-150
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20852

Dear Dr. Gyarfas:

NDA 18-035 Technetium Tc99m MDP Kit

Reference is made to the telephone conversation on October 4, 1977 between Ms. Kathleen Jongedyk, FDA chemist, and Dr. R. F. Randall, Merck Frosst Laboratories, regarding the chemistry review.

We enclose with this letter the revised finished product (Stannous Methylene Diphosphate Complex) specifications and test methods for both labelling efficiency and in vivo behaviour.

As requested by Ms. Jongedyk, copies of this protocol are being sent to the two FDA test laboratories, to be used for the testing of the finished product samples in their possession.

Sincerely yours,

Charles P. Balant, Ph.D.

/bas

Attachments
Certified No. [redacted]

cc: Mr. Ed. Baretta, [redacted] /Att. - 197704
Mr. Leonard Ford, HFD-420/Att. - 197705
Ms. Kathleen Jongedyk, HFD-150/Att.- 197706

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