# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 017024

## PHARMACOLOGY REVIEW(S)

April 21, 1971

ORIGINAL PHARMACOLOGICAL REVIEW OF NDA 17-024 (REVIEW #1)

NDA: 17-024

NAME OF THE APPLICANT: E. R. Squibb and Son

NAME OF THE DRUG: "Strotope"; Strontium Nitrate $Sr^{85}$ Injection; $Sr^{85}(NO_3)_2$

CATEGORY: Diagnostic Radiopharmaceutical

COMPOSITION: Each ml contains about 0.22 mg Strontium$^{85}$Nitrate; 1 mg methyl and propyl parabens; 9 mg NaCl; NaOH and/or HCl to get to pH 3.2-6.0 and water for injection q.s. Radioactivity at time of calibration 10-100 uCi/ml. Specific ectivity 500 uCi $Sr^{85}$mg Strontium. The physical T½ of $Sr^{85}$ is 64 days and produces in its decay to stable $Rb^{85}$a gamma emission of 0.514 mev and X-radiation of 0.012 mev. $Sr^{85}$ is produced by neutron bombardment of $Sr^{84}$ which here seems to be done by the reactors [redacted]

RELATED F. R. ANNOUNCEMENT: January 27, 1971 36 FR 1274

RELATED AGENTS BY USE: $Sr^{87m}$, $Ca^{45}$, $Ga^{67}$, $F^{18}$ and 68, $Ba^{140}$

[redacted]

RELATED INDs: None--Available at the present time under AEC regulations.

[redacted]

CLINICAL INDICATIONS AND DOSAGE: To be used for the external scintiscanning of bone for the detection of tumors and areas of increased osteoblastic activity such as found in fracture sites, osteomyelitis and epipheseal lesions. The usual recommended adult IV dosage is 50-100 uCi. Suggested dose for children to age 20 is 20-50 uCi. Scanning is usually recommended to be done at 24-72 hrs. after drug administration as then 50% of the non-deposited $Sr^{85}$ has been cleared from the body (and thus has reduced the background radiation) enabling better visualization of the lesion.

TOXICITY: (for additional items see also NDA 16-698 $Sr^{85}(NO_3)_2$ from Neisler Labs.) Acute single dose (from Spector's Handbook of toxicology)

| RAT | IV MLD | IV LD | IP $LD_{50}$ |
|---|---|---|---|
| For acetate salt | - | 238 | - |
| Bromide | 500 | - | 1,000 |
| Chloride | 400 | | |
| Fluoride | | | |

425

| | IV MLD | IV LD | IP $LD_{50}$ |
|---|---|---|---|
| Iodide | 500 | | 800 |
| Lactate | | | 900 |
| Nitrate | | | 540 |

In an early study by Haldane 60 g of $Sr\ Cl_2 \cdot 6H_2O$ where injected by one man. This resulted in violent diarrhea but there was full recovery.

MICE - 10 males as part of safety test injected IV with 0.48 mg/kg cold $Sr(NO_3)_2$ as .025 mg/ml in water. Temporary loss of strength reported.

Mice - 20 males as part of a safety test injected IV with 10 mg.kg as a 0.5 mg/ml in saline solution. No toxicity noted.

DOGS - .048 or .096 mg/kg injected IV as a 0.25 mg/ml solution in water. A transient tachycardia was noted at the higher dose. 4 other dogs injected IV with 2.5 mg/kg in saline had no adverse effects.

SUBACUTE/REPEATED DOSE:

MAN - 47 mg strontium lactate injected IV daily for 5 days as 23.5 mg Sr/ml into 2 investigators as part of a metabolic study [redacted] Only adverse effects noted were on the 5th day when a contaminated solution was used. 33-57% of the strontium lacatate was excreted during the 2 day collection period after the last dose and during the trial. 90% of this was in the urine.

CHRONIC TOXICITY DATA: No data supplied or required.

REPRODUCTION/LACTATION/PLACENTAL TRANSFER ETC.: In mice the $Sr^{85}$ given to dams and deposited in bone mobilized during pregnancy and passed the placental barrier to the fetus resulting at times in higher specific activity levels of the fetal than maternal bone. Considerable Sr is also transferred during nursing. 12-20% of that injected into nursing mouse dams was recovered in the nursing offspring. In cows after a single IV dose 9% of the radioactive Sr was reserected in the milk over a 5 day period.

Normally human fetal bones contain about 0.016% strontium and adult bones about 0.024% based on a cadaver study by [redacted] The difference is ascribed to the different degree of mineralization.

In a monkey study it was shown that $Sr^{85}$ is able to pass freely from the dam to the fetus and back and that after an injection into the fetus or the dam, there is a similar Sr disappearance rate after the initial equilibration period.

In studies trying to determine the rate of placental transfer of Calcium and Strontium it was shown that there seems to be a preference of Ca over Strontium. This was more pronounced in experimental animals ie rabbits and rats than in man.

PHARMACOLOGY: Normal weekly excretion of stable Strontium was measured in 2 investigators [redacted] and found to be about 30 mg. Presumably therefore there is also a weekly intake of 30 mg. However in studies in which $Sr^{85}$ had been given orally it was poorly absorbed and largely excreted in the feces. In mice only 6-14% of an oral dose was absorbed while 13-30% of an oral Ca dose was assimilated. High Ca content of the diet reduced Sr uptake. The binding of plasma proteins with $Ca^{45}$ was shown to be more pronounced than for $Sr^{85}$. In plasmas from man, dog and horse this averaged about 57% bound Ca and 47% bound Sr. In cows, sheep and rats the comparable figures were 69% of bound Ca and 60% Sr. In man after a single dose injection IV 0.5% of the dose was accounted for in the plasma at 50 hrs and 30% had already been excreted in the urine and 1% in the feces. By 100 days about 31% of the dose was excreted and by one year 86%.

In a rat study with Sr injected IP sacrifices at 1 hour, 1,2,4 and 16 days indicated by autoradiographic technique that localization was greatest in the epiphysis and metaphysis of long bones and the dentine of teeth.

The Sr content of various bones from a single individual fe femur rib, vertebrae and parietal bones was relatively constant. Samples from various cadabers suggested that this ranged in individuals through out life from 0.015 to 0.055% with no age related pattern.

In Paget disease a relative 7:1 ratio of isotope uptake was attained by Klein between affected and normal bone at 1-2 days.

DOSIMETRY CONSIDERATIONS: The total radiation dosage of $Sr^{85}$ to the bone and the whole body is far larger than that calculated for the "newer" agents, $F^{18}$, and $Sr^{87m}$. This is largely due to the difference in $T_{\frac{1}{2}}$ physical between the agents with $Sr^{85}$ having 64 days compared to 1.83 and 2.8 hrs for the $F^{18}$ and $Sr^{87m}$ respectively. The short half life makes repeat scans very possible while with $Sr^{85}$ the interval between scanning procedures must be considerably longer. The newer agents tend to give a "quick and dirty" picture having a scanning requirement that is shortly after administration while with the $Sr^{85}$ the patient may be scanned at several days after administration. This delay produces a "more refined" picture with greater difference between the lesion and background. However, by use of $Sr^{85}$ there is also an increased radiation cost to the patient. A table comparing the absorbed dose fractions in IND 5373 (SKI for $F^{18}$) suggests that with 1 mCi doses of the $Sr^{87m}$ and $F^{18}$ but using 0.1 m Ci of $Sr^{85}$ the exposure ratio for the skeleton between $\frac{Sr\ 85}{F\ 18}$ is 19 and $\frac{Sr\ 85}{Sr\ 87m}$ is 34 while the exposure ratio of the whole body is $\frac{Sr\ 85}{F\ 18}$ is 26 and $\frac{Sr\ 85}{Sr\ 87m}$ is 65. This is under conditions where the total absorbed dose of $Sr^{85}$ $D_{beta\ and\ gamma}$ to the skeleton was 5.5 rads and $D_{beta\ and\ gamma}$ to the whole body 1.3 rads. These calculations are somewhat at variance and higher than those reported in the labelling in tabular form from assorted references. A more detailed description of how to calculate the dosimetry seems indicated in the package insert.

EVALUATION AND COMMENT: Strontium$^{85}$ is available from most of the radiopharmaceutical suppliers at this time [redacted]

While newer shorter half-life isotopes are in part replacing $Sr^{85}$ for bone scans it is still very widely used and has over the years demonstrated its relative safety and efficacy. From the standpoint of pharmacology we feel adequate data is available from preclinical and human studies to demonstrate safety of the chemical substance. The radiological exposure while larger than that for the newer agents is still within currently acceptable limits. For a single dose administration agent such as this one adequate information regarding distribution during pregnancy and lactation is presented to justify the restrictive labelling as found in the package insert. The labelling itself seems in need of revision as present policy does not sanction an enumeration of 38 references, the guidelines to photoscanning section seems excessively long, the interpretation section seems also excessive and the absorbed dose discussion in the dosimetry section fails to give detailed calculations. The limits set in the formulation, 10-100 uCi/ml seem rather large for a product with a half life as long as this one.

When the normal Sr turnover by man is about 30 mg per week as measured by urine and fecal analysis we feel chemical dosages of 0.2 mg on a single dose administration basis can be tolerated.

RECOMMENDATION: From the standpoint of pharmacology the NDA is acceptable if certain labelling adjustments are made.

MANFRED M. HEIN

Manfred M. Hein
Pharmacologist

cc:
Orig.
Dup.
Trip. (NYK-DO)
BD-100
BD-150
R/D Endorsed by DJRichman:4/21/71
BD-150/MMHein:4/21/71
Final typed by alt:6/10/71

APPEARS THIS WAY ON ORIGINAL

December 30, 1971

SUPPLEMENTAL PHARMACOLOGIST REVIEW OF NDA 17-024 (Review #2)

NDA: 17-024

Applicant: E. R. Squibb & Sons, Inc.
New Brunswick, New Jersey

Name of Drug: Strotope; Strontium 85 Nitrate Injection

This NDA was reviewed for pharmacology on April 21, 1971 (M. M. Hein) when it was found to be approvable from the standpoint of pharmacology. Changes in labeling, however, were deemed desirable.

Submission of September 9, 1971 is partly in response to our non-approvable letter of August 17, 1971 and is labeled a "Resubmission." It contains product specification data of [redacted] relating to nuclidic purity.

Submission of October 29, 1971 is also in response to our N/A letter of August 17, 1971 and contains new labeling. Reference to Industry-FDA conference is also made. Submission contains new labels and labeling and is also considered as a "Resubmission." (The question arises from when the 180 d countdown commences, November 3 or September 10, 1971 the two receipt dates in B.D.)

Comments on labeling:

1) Isotopes should be calibrated at the factory and that time should be the calibration time, not some arbitrary later time. This is important for figuring expiration date and avoids such confusion as the "Decay Table" (Table I) presents by precalibration and postcalibration decay factors.

2) On page 2 of labeling "Strotope (Strontium Nitrate $Sr^{85}$ Injection) contains less than 2% $^{89}Sr$ . . ." 2% in terms of radionuclidic concentration, radiation energy emitted or what terms? The sentence following about ratio of $Sr^{89}$ and $Sr^{85}$ seems to be padding as the relative half lives are 64 and 50.4 d and the ratio will not very appreciatively change in a product of limited expiration dating (30 d) period.

Recommendation: NDA remains approvable from standpoint of pharmacology with minor changes in labeling.

Manfred M. Hein, Pharmacologist

cc:
Orig. NDA 17-024
Dup.
Trip. (NYK-DO)
BD-100
BD-150
R/D Endorsed by: DJRichman 12/30/71
BD-150/MMHein:aes 2/7/72

APPEARS THIS WAY ON ORIGINAL

## SUPPLEMENTARY PHARMACOLOGY REVIEW NDA 17-024

April 3, 1973

NDA 17-024

Name of Applicant: E. R. Squibb & Sons

Name of Drug: Stretope

With the 3/23/73 submission of an acceptable package insert (in conformity with our model labelling essentially and corporating comparative dosimetry on $F^{18}$) this NDA is now approvable from the standpoint of pharmacology.

Manfred M. Hein
Pharmacologist

cc:
NDA 17-024 Orig.
Dup.
Trip.(NYK-DO)
BD-100
BD-150
BD-150/MHein:4/3/73
Final typed dcg:4/6/73
BD-52

APPEARS THIS WAY ON ORIGINAL

June 6, 1974

SUPPLEMENTAL PHARMACOLOGIST REVIEW OF NDA 17-024

NDA: 17-024

NAME OF APPLICANT: E.R. Squibb & Sons Inc.
New Brunswick, N.J. 08903

DATE OF APPLICATION: April 4, 1971

NAME OF DRUG: Strope (Strontium Nitrate - $Sr^{-85}$ Injection)

CATEGORY: Bone imaging agent

COMPOSITION: Aqueous solution of 0.22 mg $^{85}$Sr nitrate, 1 mg methyl propyl parabens, 9mg NaCl, and water to 1 ml, pH 3.2 to 6.0

RELATED INDs: None

[redacted]

PRECLINICAL STUDIES: Previously reviewed

DOSIMETRY: Previously reviewed. The purpose of this review is to amend radiation dose values contained in the draft package insert.

COMMENTS AND EVALUATION: This application was reviewed previously on April 21, 1971. December 30, 1971 and April 3, 1973. In order to confirm and amend values for radiation doses that are contained in the draft package insert, the following recommendations are made.

RECOMMENDATIONS: Request "The following absorbed radiation dose values resulting from use of 100 microcuries of $^{85}$Sr are recommended for inclusion in Table III of the draft package insert: Skeleton, 1.8; testes, 0.83; ovaries, 0.85; whole-body, 0.65 rads. The following absorbed radiation doses resulting from use of 4 millicuries of $^{18}$F are recommended for inclusion in Table III of the draft package insert: Skeleton, 0.44; testes, 0.23; ovaries, 0.24; whole-body, 0.18 rads. The $^{85}$Sr radiation dose values are based on percentage uptakes of about 50% in skeleton and whole-body, 0.5% in testes, and 0.1% in ovaries.

Bergene Kawin, Ph.D.

cc;
NDA: 17-024
Orig. Dup. Trip.
HFD-100, HFD-150
HFD-150/BKawin: G.M. 7-17-74

APPEARS THIS WAY ON ORIGINAL

# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: 017024

## ADMINISTRATIVE/CORRESPONDENCE DOCUMENTS

NDA 17-624

AUG 17 1971

AF 9-561



E. R. Squibb & Sons, Inc.
Attention: Paul H. Roberts, M.D.
Georges Road
New Brunswick, New Jersey 08903

Gentlemen:

Reference is made to your New Drug Application dated April 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Stratope (Strontium Nitrate-Sr 85 Injection).

We have completed our review and find that the information presented is inadequate and the application is not approvable. The deficiencies may be summarized as follows:

Under section 505(b)(4) of the Act, the application fails to provide adequate information with regard to the product obtained from the [redacted]. Specifically, the phrase "exclusive of" in describing radiopurity can be interpreted in different ways. Clarification is requested.

Under section 505(b)(6) of the Act, the application fails to provide an adequate immediate container label. In this regard, the meaning of "prime container label" and "assay" should also be clarified.

In addition, the proposed package insert exhibits a number of deficiencies. We suggest that you arrange a conference between your representatives and members of the Division of Oncology and Radiopharmaceutical Drug Products in order to arrive at adequate and acceptable labeling.

This file is now closed. If you wish to reopen it, the submission should be in the form of an amendment to this application, adequately organized, which represents the information necessary to remove all deficiencies we have outlined.

If you do not agree with our conclusions, the law provides you an opportunity to obtain a hearing, if requested within 30 days from the date of issuance of this letter, on the question of whether the application, as you have presented it, is approvable. This may be obtained by a written request for filing over protest, as authorized by section 130.5(d) of the regulations. Notice of opportunity for a hearing will be published in the FEDERAL REGISTER.

Sincerely yours,

Henry E. Simmons, M.D., F.A.P.H.
Director
Bureau of Drugs

NOT APPROVABLE
cc:
Orig., Dup., Trip. (NYK-DD)
BD-100
BD-150
BD-22
BD-242
BD-226
BD-1
BD-150/BKagan:7/28/71
R/D Endorsed by CFBruening:7/29/71; HWHeln:7/29/71; DJRichman:8/3/71
ELChacalos:8/3/71; BLJones:8/3/71; ELMeyers:8/3/71
Final typed by slt:8/10/71

APPEARS THIS WAY ON ORIGINAL

MEMO OF TELEPHONE CALL

October 31, 1972

Between: Charles L. Kroll, Ph.D.
Technical Director, Drug Regulatory Affairs
E.R. Squibb & Sons, Inc.
New Brunswick, New Jersey
(201) 545-1300

and

Mr. Benjamin Kagan, Chemist
DORDP, OSE BD-150

Subject: NDA 17-024

Dr. Kroll was called in order to request additional information with regard to assay methods.

We discussed the amendment of September 15, 1972, which provides a detailed description of a radiochemical purity test. It was pointed out to Dr. Kroll that a similar detailed description would be required for the methods used to check other specifications of the finished dosage form, such as radioactivity and radionuclide identity. This information would expedite the methods validation.

Dr. Kroll agreed to provide such additional information as was necessary for this NDA. Also, he will check their other radiopharmaceutical NDA's and submit additional information where needed.

Benjamin Kagan, Chemist

cc:
NDA 17-024 Orig.
Dup., Trip.(NYK-DO)
BD-100
BD-150
BD-150/BKagan:10/31/72
Final typed deg:10/31/72

APPEARS THIS WAY ON ORIGINAL

NDA 17-024
Strotope
E. R. Squibb & Sons

April 4, 1973

RECOMMENDATION OF THE DIVISION DIRECTOR

The application is recommended for approval under Section 505(b) (1), (2), (3), (4), (5) and (6) of the Act. The supervisory staff of the Division of Oncology and Radiopharmaceutical Drug Products concurs with the reviewing personnel of this application with regard to the conclusions and recommendations for approval.

Strotope (Strontium Nitrate Sr 85 Injection) distributed by E. R. Squibb & Sons and labeled with reactor produced Strontium 85, is available for use as a single dose diagnostic agent for the purpose of scintiscanning of bone. Efficacy and safety in clinical use has been established by virtue of the following:

1) The agent has been marketed under investigational labeling for many years by this applicant and is recognized by experts as being a useful agent with a low incidence of drug interactions and adverse side effects.

2) Review of model labeling has been made by panels of the FDA Medical Advisory Committee on Radiopharmaceuticals and several FDA consultants and they concur with the proposed indication and directions for use.

3) The agent is included for use in "Bone scans on patients with diagnosed cancer" in the FR announcement of November 3, 1971 (also identified as Title 21 Section 130.49 36 FR #212 page 21036-8.

4) The agent is included on the AEC list of well established radiopharmaceuticals for bone scanning.

5) The formulation consisting of 10-100 mCi/ml normal saline, methyl and propyl parabens (1 mg/ml total) and 0.22 mg/ml Strontium Nitrate is not expected to induce a pharmaceutical effect.

6) There is an extensive body of published literature on Sr 85 which in part has been summarized and included in the NDA. In those studies where Strotope was used (as compared to a competing supplier) this has been indicated. IV doses generally were 100 uCi in the 56 female and 62 male subjects

aged 13 to 91 specifically identified. Most of the subjects where in 40 yrs of age group or older.

7) Strontium 85 has been available for many years commercially as a bone scanning agent but using investigational labeling under the 1963 exemption.

Labeling has been reviewed and was found to comply with current labeling format and with model labeling furnished to the supplier by FDA. Under dosimetry comparative exposure from the use of $F^{18}$ will be included to demonstrate the relative comparative safety of the two commercially available and NDA approved agents with identical indication.

Earl L. Meyers, Ph.D., Director
Division of Oncology and
Radiopharmaceutical Drug Products
Office of Scientific Evaluation
Bureau of Drugs

SUMMARY OF BASIS OF APPROVAL

April 4, 1973

We recommend that NDA 17-024 Strotope (Strontium Nitrate Sr 85 Injection) be approved on the basis of the following summaries:

I. MEDICAL:

Safety and efficacy of firm's strontium nitrate Sr-85 has been established in studies with 118 patients. Sr-85 is also identified in section 130.49, Title 21, CFR as well established as a bone scanning agent. This radiopharmaceutical has been used successfully for years as a bone scanning agent and there is an extensive literature supporting this use and delineating its relative safety.

Approval is recommended.

Bryant L. Jones, M.D.
Deputy Director
Supervisory Medical Officer

II. PHARMACOLOGY:

The Federal Register announcement Title 21 130.49 has established Strontium Nitrate Sr 85 Injection to be safe and effective for "Bone scans on patients with diagnosed cancer." It has been used extensively for bone scans of all types for many years using investigational labeling. At the suggestion of and on review of model labeling the FDA Medical Advisory Committee on Radiopharmaceuticals the labeling has been broadened to include all bone scans.

Due to the large difference in radiation exposure of the patient between $F^{18}$ and Sr 85 comparative dosimetry is being included in the labeling.

In view of the human experience:

1) Preclinical studies on this formulation have not been requested.

2) The chemical toxicologic potential of the drug dosage form (including any excipients) by the clinical route of administration (IV) is adequately defined to suggest that it is reasonably safe for clinical use.

3) The total chemical dose is about 0.22 mg of Strontium Nitrate I.V. which will not raise blood Strontium levels significantly as it represents a small fraction of that usually taken in by the oral route. Strontium is readily absorbed from the G-I tract.

4) Dosimetry estimates have been made based in part on the Medical Internal Radiation Dose publications and recognized methods of calculation have been employed. A comparison with F 18 will be provided.

David J. Richman, Ph.D.
Supervisory Pharmacologist

III. CHEMISTRY:

Manufacturing and controls information Satisfactory

Stability Studies - support 3 month expiration date. Satisfactory.

Method Validation - Satisfactory

Labels and Labeling - Satisfactory from viewpoint of manufacturing controls.

Recent inspection found facilities and manufacturing practices in agreement with provisions of the NDA.

Application is satisfactory, based on manufacturing controls.

Charles F. Bruening
Supervisory Chemist

cc:
NDA 17-024 Orig., Dup., Trip.(NYK-DO)
BD-100, BD-150, BD-106, BD-242
BD-150/ELMeyers, BLJones, CFBruening, DJRichman, BKagan, EHChacalos, MMHein
Final typed deg:4/6/73

APR 24 1973

NDA 17-024

AF 9-561

E. R. Squibb & Sons, Inc.
Attention: Norman W. Lavy, M.D.
Georges Road
New Brunswick, New Jersey 08903

Gentlemen:

Reference is made to your new drug application dated April 2, 1971 submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for the preparation Stratope (Strontium Nitrate Sr 85 Injection).

We also acknowledge receipt of your additional communications dated September 9, 1971, October 29, 1971, June 6, 1972, September 15, 1972, November 15, 1972, December 19, 1972, January 26, 1973 and March 23, 1973. These submissions amend the application, with a proposed draft of package insert provided by the March 23 submission.

We have completed the review of this application as submitted with draft labeling. However, before the application may be approved, it will be necessary for you to submit final printed labeling. The labeling should be identical in content to the draft copy. If additional information relating to the safety or effectiveness of this drug becomes available before we receive the final printed labeling, revision of that labeling may be required.

Please submit twelve copies of the printed labels and other labeling.

In addition, we would appreciate your submitting in duplicate the advertising copy which you intend to use in your proposed promotional or advertising campaign. Please submit one of the copies directly to the Division of Drug Advertising with a copy of the package insert.

Sincerely yours,

J. Richard Crout, M.D.
Director
Office of Scientific Evaluation
Bureau of Drugs

cc:
Orig., Dup., Trip.(KAN-DO)
BD-100, BD-150, BD-242, BD-106
BD-150/BKagan:4/6/73
R/D Endorsed by CFBruening:4/6/73
MWHein:4/6/73
DJRichman:4/16/73
BLJones:4/6/73
EHChacalos:4/6/73, ELMeyers:4/16/73
Final typed by slt:4/17/73
APPROVABLE

APPEARS THIS WAY ON ORIGINAL

BEST POSSIBLE COPY