CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 017024

MEDICAL REVIEW(S)

24 June 1971

INITIAL MEDICAL SUMMARY OF ORIGINAL NDA 17-024

NDA: 17-024

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

Name of Drug: Trade: Strotope
Generic: Strontium Nitrate ^{85}Sr solution

Dosage Forms and Route of Administration: Isotonic solution of strontium nitrate at a concentration of less than 0.22 mg/ml and 10-100 microcuries/ml.

Dosage is 50-100 microcuries for adults and 20-50 microcuries for patients under 20 years.

To be given intravenously.

Physical Properties of Radionuclide: Strontium-85 has a half-life of 64 days and decays by electron capture to stable Rubidium 85 emitting 0.514 MeV gamma ray, a .013 MeV x-ray and some (less 1%) internal conversion electrons. It is produced by following reaction ^{85}Sr (N, Y) ^{86}Sr.

Category or Use: Diagnostic radionuclide used in bone scanning, particularly in detection of bone tumors and lesions.

Type and Date of Submission: Original NDA dated April 2, 1971.

Material Reviewed: Volumes 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 of above submission.

Chemistry Summary: Under Review

Pharmacology Summary: Under Review

Clinical Evaluation:

Introduction: ^{85}Strontium is one of several bone-seeking gamma emitting nuclides such as ^{47}Ca, ^{18}F and ^{87m}Sr which have been used in diagnosis of bone tumors by scanning techniques.

According to sponsor ^{85}Sr has been available for bone scanning since 1960. Its use in the localization of bone lesions depends on the higher count rates after ^{85}Sr injection found over fractures, tumors, osteomyelitic and epiphyseal lesions than over normal bone. According to Charkes et al (1966, Am. J. Roentgenol 96: 647-650) radiostrontium is deposited in immature astroid tissue. formed in reaction to invading malignant cells which is supposedly the mechanism of bone tumor localization.

The AEC has limited the use of ^{85}Sr to bone scans on patients with diagnosed cancer, probably because the absorbed dose to bone is rather high, up to 4.6 rads for the usual 100 microcurie adult dose. However, the AEC does not relate this use limitation to any specific dose, has nowhere justified it to our knowledge, and this restriction is quite at variance with present medical practice. A further consideration is that ^{85}Sr has been in use since 1960 and quite widely in more recent years, yet no clear cut adverse reaction due to its use has been reported to our knowledge. If any should appear later as a result of late radiation effects relevant changes could be made at that time in insert to restrict its use. But at the present stage the evidence does not support limitation of use as recommended by AEC.

There are three groups of indications listed in proposed insert:

(1) "Early detection of malignant bone tumors. Photoscans with ^{85}Sr can detect metastases to bone prior to any demonstrable roentgenographic bone change."

(2) Differential diagnosis between (a) myelomas and other osseous metastases, (b) dormant and active metastases of some tumor and (c) pathologic from traumatic fracture.

(3) Planning of treatment and assessment of therapy, of operability, progress of disease.

Six investigators reported on studies in 113 cases using Squibb's strontium nitrate (Strotope). The method used by all six was more or less the same: 50-100 microcuries were given I.V. to adults with suspected bone areas scanned. 24-48 hours later. This interval allows 50% of body strontium not deposited in bone to be excreted via kidney or bowel. In scans involving lower spine and pelvis bowel and bladder are emptied beforehand.

1. Studies by [redacted]

In 25 patients with suspected bone lesions scans were good in all cases, none were excellent, fair or poor. 12/25 scans showed positive findings, 13/25 negative. Investigator claims that in 90% of the time results obtained were consistent with established diagnosis. This claim could not be verified because in every case report form the evaluation of the results and the diagnosis were left blank.

Conclusion: If this perfunctory investigator may be believed the only proof provided for his studies was that the firm's Sr-85 produces 'good' bone scans and some 'positive findings' presumably around areas of tumor tissue (but not always, pt. N.n, p. 12-1019.

2. Studies by [redacted]

In two patients where a diagnosis of neoplasma was established by biopsy positive scans were obtained. Two other neoplastic patients showed negative scans.

Conclusion: Study too limited to be conclusive but tends to verify efficacy of firm's ^{85}Sr to detect and localize bone tumors.

3. Studies by [redacted]

In 8 cases of scanning for bone neoplasma comparisons were made with x-ray findings and found to agree in seven cases. One was somewhat dubious because of poor scan. Only negative finding was in a case of thrombophlebitis.

Conclusion: Shows scan findings of bone lesions correlate well with x-ray findings.

4. Studies by [redacted]

In 34 patients (mostly with neoplasmas) results of bone scans were good to excellent in all cases with 90% accuracy. Positive scans obtained in 23/34 cases of which two had negative x-rays. Three reports failed to record any clinical information or results of administered isotope. Investigator believes ^{85}Sr is of great value in evaluating bone pain in known cancer patients and in outlining x-ray therapy but because of its long half-lives it should be reserved for known cancer patients. He notes that ^{85}Sr scintiscanning may reveal less developed lesions in advance of positive x-ray findings.

Conclusion and Evaluation: Further evidence indicating that firm's ^{85}Sr is efficacious in detection of bone lesions occasionally presenting findings not shown on x-rays. However, one wonders why three patient report forms were not filled out.

5. Studies by [redacted]

Nineteen case reports of patients with primary or bone neoplasia confirmed by bone biopsy were summarized by firm (not by investigator). Scans were excellent in 11, good in 6, and fair in 2 cases. Seventeen demonstrated areas of increased uptake over sites of bone disease, 12 of which were not seen on x-ray. Two cases with area of pathology showed no radioactive uptake.

In another study on 15 patients (only 7 case histories presented in author's summary) the x-ray and scan both demonstrated the abnormality in 9 cases. In one case the scan was positive, the x-ray negative. In seven cases scan revealed more bone involvement than the x-ray. In four cases scan was

negative and x-ray positive. In his typescript the investigator points out that bone decalcification must reach about 50% before evident on x-ray films and that asteeblastic metastases are better visualized than astealytic lesions.

Conclusion: Good study because bone biopsies and comparisons of scans with radiographs were done. Serume phosphatases, calcium and phosphorous were done on most patients.

6. Studies by [redacted]

In 19 cases with malignancies of prostate and suspected bone involvement 14 patients had positive scans, 9 of which had negative x-rays. Three of the 14 had elevated acid phosphatases. It is interesting to note that 9 cases had negative bone biopsies while the scans were positive. Scans were usually good or excellent. Serum phosphatases and other lab data were collected for each patient. The only obvious defect was the absence of the investigator's own summary and work-up of raw data.

Conclusion: Convincing study though work-up of data done by firm.

II. Published Literature: Several reprints of preclinical and clinical studies were submitted. Thirty-eight supported statements in package insert and listed therein as references. These will be considered in evaluation of proposed insert. Only those reprints were abstracted which appeared to made a significant contribution to safety or efficacy.

A. Reprints under Clinical Reports (Vol 1.y)

1. Bauer, G.C.H. et al (1959) External Counting of ^{47}Ca and ^{85}Sr in studies of localised skeletal lesions in man. J. Bone o Joint Surg. 41B:558-580.

In a study of 75 patients radioactivity for both kinds of radionuclides was found higher over skeletal lesions like fracture, metastatic cancer, eosinaphilic granuloma, chondroma, asteomyelitis and Paget's diseases which was interpreted as an increased rate of bone turnover.

2. S. Kofman et al (1963) The use of ^{85}strontium in the evaluation of bone metastases, J. Nucl. Med. 4:9-17.

Vertebral scans were done in 9 patients with known asseous metastases, in 6 with 'normal' bones, in another 6 with suspected metastases and in 3 with non-metastatic bone lesions. Eight out of the first nine and 4/6 of those with suspected metastases had positive scans. All other scans were normal. It was concluded that ^{85}Sr uptake is higher in mixed or asteoblastic metastases, but in astealytic metastases uptake may be increased or normal.

3. G. L. DeNardo et al (1966), Detection of bone lesions with strontium-85 scintiscan, J. Nucl. Med. 7:219-236.

Scintiscans with ^{85}Sr were done in 50 patients with various bone diseases. It was pointed out that correct interpretation of bone scans required knowledge of normal sites of increased radioactivity, viz. at ends of long bones, around acetatula and sacroiliac joints, over vertebrae, carpal and tarsal bones. Abnormal scans were found in 32/50 pts. which included 17 with metastases, 9 with osteomyelitis, 2 with primary bone neoplasms, 2 with lymphoma, one with Gaucher's and another with Paget's disease. Significant were the comparisons with radiographs as given in table below:

	Scintiscan	
Radiograph Finding	Positive	Negative
Positive	16	0
Negative	14	10
Questably Positive	2	8

B. Reprints from Preclinical Reports (Vol. 1.3)

These dealt mostly with animal studies but some were referred to in insert.

III. Metabolism and Safety Considerations:

^{85}Sr as a chloride is excreted primarily through the kidney. At 50 hours after i.v. injection 30% of dose found in urine and 1% in feces; at 100 days 81% had been eliminated in feces and urine (Bishop et al (1960) Int. J. Rad. Biol. 2:125-142) (Other metabolic studies also cited).

It appears that tracer amounts of strontium rapidly traverse the placenta in both directions. (MacDonald et al (1962) Radiation Res. 17:752-766).

Dosimetry: In insert radiation dose of 100 microcuries ^{85}Sr was given as 0.6 Rad to whole body and 1.6-4.6 rads to bone on the basis of references, but not showing the actual calculations. Radiation dosages of various radioactivity doses are given on basis of literature references none of which present details and assumptions used in calculations.

IV. Evaluation of Package Insert:

The package insert is overly long, verbose, repetitious, confuses by an excess of superfluous detail and mode of presentation, contains too many references (38) and tends in places more to confound than inform. In what follows paragraphs to be included in an eventual letter are numbered and placed in quotes.

Description Section: First two paragraphs are acceptable.

Physical Properties: "Under the subsection 'Biological and effective half-life', the statements made are not substantiated by given references which appear inappropriate. These should be corrected, or explained."

Reason: The statements that 70% of i.v. dose is excreted in 20-30 days is due to Bishop et al (1960) Int. J. Rad. Biol. 2: 125-142, not the given reference. The additional statements e.g. T½Biol.=600-843 days which contradict the above could not be found in the cited reference, viz Bauer (1968), Clinical use of Radioactive isotopes in orthopedices, ref. #18.

Actions:

2. "The statement under Actions reading 'Lesions smaller than 1cm. are difficult to visualize by conventional roentgenographic techniques but may become evident by scanning with ^{85}Sr' could not be found in supporting reference. Either substantiate or delete."

Reason: Support for claim could not be found in the general supporting reference (Wagner, Principles of Nuclear Medicine) and its validity is open to doubt in any case.

Indications:

3. "Under Indications delete material under subsection entitled, 'Early detection of malignant bone tumors'. Replace with,

DRAFT LABELING

Reasons: ^{85}Sr-Scan also helps detect primary bone tumors which was implied in subsection headings but not mentioned in succeeding paragraph. Positive x-rays and negative scans are seen in rapidly destructive osteolytic lesions (Sklaroff et al, 1964; Diagnosis of bone metastases by photoscanning with strontium-85, J.A.M.A. 188:1.4). The two statements one negative phosphotase findings and false bone biopsies are supported by a paper dealing only with prostate metastases. This was not specified. Since this subsection deals with bone tumors in general it would appear to the reader that the deleted statements are generally applicable which without a more general and extensive empirical proof is not acceptable.

4. "Under Indications-section delete subsection entitled, 'Differential diagnosis' and all material in it."

Reason: Wordings and statements are taken from a third-rate review article by G. H. Bauer (1966) (in Radioactive Pharmaceuticals AEC symposium, ed. by G. A. Andrews) who failed to document with data or ref-

erences his claims, e.g. that bone scans can and in differentiating between melanomas and asseous metastases or between active and dormant ones.

Support for claim that scans may aid in the differentiation of pathologic and traumatic fractures was not provided and seems tenuous at best. Since firm has failed to support these assertions with objective evidence they must be deleted. The cited reference consists only of unsupported assertions.

5. "Under Indications change first sentence of third subsection, 'Planning of treatment and assessment of therapy', to read: DRAFT LABELING

Reason: The word 'diagnosis' may be confused with differential diagnosis when what is really meant is detection . The use of the term 'bone lesions' brings out the fact that positive scan findings may or may not be neoplastic.

6. "Under Indications-section delete statement reading 'Determination of the presence of bone metastases may serve as a criterion of inoperability (e.g.....) or may aid in the choice between radiation and chemotherapy (e.g.....)' and the first two words, 'More precise' of the succeeding sentence".

Reasons: The first statement is strictly speaking not an indication per se, but elaborates possible inferences on medical judgements that may follow detection of bone tumors. In the supporting references for this statement the deleted statements appear as opinions, not as demonstrated facts. Moreover, the firm has generalized by giving as mere examples the only particular diseases considered when these opinions were formulated and fails to supply substantial evidence supporting the broader generalizations.

The term 'more precise' is comparative but no comparison is provided or proof of ^{85}Sr greater precision in localizing bone tumors if radiographs are the comparison. For example, would asteolytic lesions yielding negative scans be more precisely localized than with radiographs?

7. "Under Indications delete the phrase 'more precisely than x-rays'.

Reasons: Firm claims that scans may deliniate ammount of healing or progress of diseases bettee than x-rays which in some instances may be true but not in others. In any case the claim has not been fairly stated or proven. In other instances x-rays will be better, e.g. asteolytic lesions yielding negative scans. The statement as worded by firm is loeaded in favor of scans and in our opinion distorted and unbalanced.

Warnings: Appear acceptable

Precautions: Appear acceptable

Adverse Reactions:

8. "Delete statement under Adverse Reactions reading, 'The preparation is essentially free from chemical toxicity.'"

Reason: This is too broad a statement and not strictly true because chemical toxicity will depend on dosage amongst other unstated conditions. Moreover such a statement tends to produce over confidence and reduce alertness for possible adverse reactions.

Dosage and Administration:

An upper dose of 100 microcuries Sr-85 is recommended which is associated with radiation doses of 0.6 rad to the whole body and up to 4.6 rads to bone. The recommended doses appear to be current practice.

Dosimetry:

9. "Under Dosimetry delete first sentence reading, 'The radiation exposure to bone from a dose of 25-100 μ Ci strontium nitrate ^{85}Sr is comparable to the radiation exposure from a roentgenogrsphic skeletal survey etc.'".

Reason: The reference used to support this claim (DeNardo et al 1967, Radioisotope skeletal survey, J.A.M.A. 200:111) merely states this opinion without proving it, either by calculations or other documentation. Furthermore such a statement tends to engender a false sense of security by understressing the radiation hazards involved.

10., "The Dosimetry section should be rewritten to provide numerical calculations of radiation doses for the maximal recommended dose (100 microcuries) only.

The equations, definitions of symbols, and the numerical values used as well as the assumptions made should be clearly stated."

Reasons: The Dosimetry section as presented might confuse because most symbols in equations are not defined directly but dependent on references. Radiation doses for several administered activities are given which vary considerably and tend to confound. Without the numerical values used and the actual clsculation it is difficult to check the validity of the results.

Procedures-Section: This section, designated, 'Guidelines for Photoscanning with ^{85}Sr' by firm, is excessively long (11 closely written pages out of 25 pages of text for whole insert), verbose, diffuse, and in part misleading.

11. "Under the subsection 'Time of scanning' delete all material beginning with 'These investigators suggest that in order to formulate a diagnosis of secondary bone malignancy etc." and ending with ".... and it is usually carried out on an out-patient basis.' "

Reasons: The statement deals with an indication and is worded as if firmly established which is not the case and does not truthfully reflect the reference cited (E.J. Greenberg et al 1968, Detection of neoplastic bone lesions by quantitative scanning and radiography, J. Nucl. Med. 9:d.3). The authors are not so self-assured, for they say, "Further investigation of the local uptake patterns of normal and abnormal bone as a function of time may lead to the development of scan procedures that might possibly differentiate between malignant and certain non-malignant lesions in bone, something that is currently not possible."

Interpretation:

12. "Under the Interpretation-section delete the first three paragraphs beginning "Skeletal lesions such as . . . ' and ending .....' report this occurrence in approximately 7% of their patients'. Incorporate the first three sentences beginning 'Skeletal lesions...' and ending '....of tumor metastasis.' in Action section."

Reasons: Material in these three paragraphs deals more with actions and mechanisms and is not directly related to interpretation. Moreover most is redundant, being already discussed in the Action-section or in a subsequent section and in a fashion clearly and directly related to interpretation, i.e. table based on Charkes et al work (J.A.M.A. 206:2482 (1968)). In our judgement these paragraphs for the greater part serve no useful function except to occupy space, repeat and confuse.

13. "Under Interpretation delete sentence reading 'Charkes et al have performed bone scans ...in more than 700 cancer patients...' and the 'they' of succeeding sentence replace with "In a study of thirty cancer patients CharKes et al found etc.

Reasons: The statement and its positioning is misleading because the histopathological study referred to was actually done in 30 patients (Charkes et al (1968); the pathologic basis of strontium bone scan J.A.M.A. 206:2482). Whether the tabulated classification and results of this study should be included in Interpretation might be considered a moot point. In our judgement since comparisons are made between bone pathology, radioactivity and radiographic finding the table is properly placed and helpful in interpreting scan findings.

14. "Delete the entire interpretation section"

Reason: Deputy Director, Dr. B. Jones is of the opinion that there should not be any statement regarding interpretation anywhere in insert because this reflects the practice of medicine and the physician's training not the use of the radiopharmaceutical. We disagree with this viewpoint because in our view use of the radiopharmaceutical, even in the narrow sense, is also a part of the practice of medicine yet is retained; interpretation constitutes an essential component of proper use. Moreover, even a well trained expert in nuclear medicine may not be aware of or remember the comparative relationships between degree

of mineralization, histopathological findings, scan and radiographs as nicely presented in the table of this section particularly when one considered these are rather recent developments (1968). It's doubtful whether all specialists keep up with all developments in the literature of their speciality.

15. "The number of references listed should be limited to ten."

Reasons: Recommended in bureau memorandum dated October 29, 1969 which to our knowledge has not been rescinded. Proposed insert contains 38 references.

V. Review of References Cited in Insert: Bookds and general references excluded; references numbers of insert retained.

1. Charkes, N.D. et al. (1964), Early diagnosis of metastatic bone cancer by photoscanning with strontium-85. J. Nucl. Med. 5:168.

Bone scans with ^{85}Sr in about 90 patients with proven or suspected bone metastases whowed that in eleven patients scan was positive and x-ray negative, and in 75 others there was good agreement. The scan however frequently showed greater involvement. In six pts. the scan failed to reveal lesions that could be demonstrated by x-rays. At least three of these had neoplasms as shown by bone biopsy.

2. D. M. Sklaroff et al (1964), The detection of bone metastases by photoscanning with radioactive strontium; in Scintillation Scanning in Clinical Medicine, Philadelphia, pp. 69-86.

In 28 pts. scan positive, x-ray negative; in four cases reverse was true.

3. I. Gynning et al (1961), Localization with ^{85}Sr of spinal metastases in mammary cancer and changes in uptake after hormone and roentgen therapy, Acta Radial 55:119

Spine-scans with ^{85}Sr in 70 cases of mammary carcinoma proved to be a good complimentary method which sometimes demonstrated metastases earlier than radiographs. In palliative androgenic therapy uptake returned to normal when clinical improvement was observed.

4. N.D. Charkes et al. (1966), A critical analysis of strontium bone scanning for detection of metastatic cancer, Amer. J. Roentgenology 96:647.

An evaluation of over 350 bone scans with ^{85}Sr in cancer pts. Biopsy studies in 26 pts showed that ^{85}Sr deposits in new bone formed in reaction to cancer. In 2% of patients negative scans obtained in areas of known bone metastases.

5. E. J. Greenberg et al. (1968), Detection of neoplastic bone lesions by quantitative scanning and radiography, J. Nucl. Med. 9:613.

In a study with ^{85}Sr and ^{47}Ca on 26 pts et was found that in 11 pts with positive scans metastatic bone disease could be confirmed at site with abnormal nuclide uptake; of 13 pts with abnormal scans, nine had a non-malignant lesion at abnormal site and the other four-none; two scans were negative. Authors point out that changes incident to early bone malignancies can be demonstrated prior to radiography. The authors stress sequential scans up to five days because two of their confirmed bone malignancies showed abnormal uptake only at times greater that 5 hrs. after nuclide injection.

7. D. M. Sklaroff and N.D. Charkes (1964), Diagnosis of bone metastasis by photoscanning with strontium 65 J.A.M.A. 188:1.

Of 21 pts. with radiographic changes in bone, scan showed corresponding increments in strontium content. Three patients had positive scans and negative radiographs. Biopsies of two of these revealed metastases at scan positive site.

8. J. Litvak et al (1967), Strontium-85 kinetics in hypoparathyroidism at different levels of calcium intake. J. Nucl. Med. 8:60.

A mathematical study of ^{85}Sr kinetics in two controls and three patients with hypoparathyroidism. Half-life of body retention was 9-10 days for the normals, and 14-18 days for the atheis, the corresponding half-lives for serum specific activity were 2 - 2.6 days and 4.5 days resp.

9. G. C. H. Bauer et al (1958), Kinetics of strontium metabolism in man, J. Bone and Joint Surg. 40-A:171.

A mathematical study of ^{85}Sr kinetics in five 'essentially' normal men. On the average 49 percent of dose was retained 4 days after i.v. injection of ^{85}Sr.

10. H. Spencer et al (1957), Strontium-85 and calcium-45, J. Clin. Invest. 36:680.

Metabolism of orally administered ^{85}Sr studied in six patients and compared with intravenous administration in four. The main excretion pathway is the kidney irrespective of route of administration, but this varies with state of metabolism of skeleton. About 10% is excreted via the intestinal tract. About 80% of the oral dose passes unabsorbed.

11. M. Bishop et al (1960), Excretion and retention of radioactive strontium in normal men following a single intravenous injection, Int. J. Rad. Biol. 2:125.

In an 140 day study of faecal and urinary ^{85}Sr determinations it was concluded that turnover of dose is a three staged process, viz. (1) raped excretion up to 20-30 days for 70% of dose (2) an intermediate

rate process accounting for 15% with a half period of 50 days (3) a chronic retention stage (15% of dose) for which excretion is negligible.

12. D. F. Williams and W. H. Blahd (1967). The diagnostic and prognostic value of strontium-85 photoscanning in carcinoma of prostate. J. Wrology 97:1070.

In twenty patients with proven adeno carcinoma of prostate bone scans were done with ^{85}Sr and compared with radiographs. In 5/20 scan was positive while x-ray was negative. In 9 patients both were positive, and in another four both negative. X-rays were equivocal in two pts. with positive scans. Scan detected more extensive metastases than routine radiographs, and are in the opinion of the authors, far superior to serum determinations of acid or alkaline phosphatase and bone marrow biopsy.

13. C. Morgan and P. Mills (1968). Radioactive bone scans in carcinoma of prostate. South Med. J. 61:785.

Bone scans were done in 66 patients with prostatic cancer 5-8 days after receiving 75 microcuries (average) ^{85}Sr i.v. Findings were compared with other tests. Results are given in table below:

DIAGNOSTIC TECHNIQUE	NUMBER DONE	NUMBER ABNORMAL	PERCENT
Sr-85 Bone Scan	66	45	68%
X-Ray	66	17	26%
Serum Acid Phosphatase	66	22	33%
Serum Lactic Dehydrogenase	53	22	22%
Bone Marrow Biopsy	52	7	14%

Subsequent scans with ^{85}Sr were done in 13 patients six or more months later with changes noted in most patients depending one response to therapy. The scans were also used to identify sites for bone biopsies.

15. J.C. Harbert and W. L. Ashburn (1968), Radiostrontium bone scanning in Hodgkin's disease. Cancer 22:58.

Bone scans were done in 51 patients with Hodgkin's disease 3-7 days after i.v. injection of 100 microcuries ^{85}Sr nitrate. These were compared with radiographs and similar comparisons from literature as given in table below: