Memorial
Hospital of South Bend
Quality of Life

Reportable
10 CFR 35.33

December 28, 2001

United States Nuclear Regulatory Commission
Region III, Medical Licensing Section
801 Warrenville Road
Lisle, IL 605532

RE: Misadministration Report

Dear Sirs:

We have enclosed the report on three (3) misadministrations which occurred due to a dose calibrator calibration error at our radiopharmacy for a beta-emitting radiopharmaceutical, Sm-153 supplied by them in unit dosage form.

If you have any questions, please contact Dick Selle, the Nuclear Medicine Manager (219-284-3112), Nina Johnson, our RSO, or myself. Our consulting physicist who assisted with this report is Tracy King of Medical Physics Consultants can be reached at 734-662-3197. Thank you for your cooperation with this matter.

Sincerely,

David A. Hornback, M.D.

615 North Michigan Street
South Bend, Indiana 46601-1087
Website: http://qualityoflife.org

REPORT OF MISADMINISTRATION TO USNRC

Licensee's Name: Memorial Hospital
South Bend Indiana

Prescribing Physician's Name: Dr. David A. Hornback

Brief Description of Event: Three patients were administered dosages of Samarium-153 that were lower than the prescribed dosage by more than 20%.

Patient A.

Date:	06/28/2000
Prescription No.	718140
Prescribed Activity:	67 mCi Sm-153
Administered Activity:	49.86 mCi Sm-153

Patient B.

Date:	08/23/2000
Prescription No.	735173
Prescribed Activity:	68 mCi Sm-153
Administered Activity:	48.44 mCi Sm-153

Patient C.

Date:	05/11/2001
Prescription No.	816061
Prescribed Activity:	60 mCi Sm-153
Administered Activity:	45.59 mCi Sm-153

Why the Events Occurred:
Unit patient dosages of Sm-153 were ordered from Spectrum Pharmacy, Mishawaka, IN, with a requested activity for a specified time.
Spectrum Pharmacay filled these orders by withdrawing a calculated volume of Sm -153 into a 3 or 5 ml syringe from a 10 ml vial calibrated at 50 mCi/ml at noon on Wednesday. The syringes were assayed in a Capintec ionization chamber dose calibrator on a setting of 170, and the volume in the syringe was adjusted, if necessary, to produce an activity matching that requested by the ordering facility. The dose calibrator setting of 170 was determined on July 23, 1997, using a NIST traceable Sm-153 standard in a 10 ml vial. During the period December 12-20, 2001, Spectrum Pharmacy determined that the 170 dial setting was appropriate only for the 10 ml glass vial, not for a syringe. Using another NIST traceable Sm-153 standard, Spectrum Pharmacy determined that the actual activity in a syringe is 28.2% less than the activity measured on the 170 setting.

Effect on the Patients: The Sm-153 was administered for palliation of bone pain. The effect, if any, of under dosing by the 24.0% to 28.8% is not known. It

would presumably result in a more than expected number of patients not experiencing relief or experiencing less relief from their symptoms

Improvements Needed, and Actions Taken, to Prevent Recurrence: Spectrum Pharmacy, Mishawaka, has established that a Capintec dose calibrtor setting of 170 is appropriate for the 10 ml of Sm-153 received from the manufacturer. It has also been determined that a setting of 273 is appropriate for Sm-153 in a 3 ml syringe. Both vial and syringe require no geometric correction factor over the range of 0.5 to 3 ml.

The Sm-153 dosages dispensed by Spectrum Pharmacy will be determined by a subtraction technique:

a. assay 10 ml vial on 170 setting
b. draw volume required into syringe, based on desired dosage and concentration of the Sm-153 solution
c. assay remainder in 10 ml vial on 170 setting
d. record dosage in syringe by subtracting remainder assay from the whole vial assay
e. confirm dosage by assaying the syringe on the 273 setting

Since Sm-153 is primarily a beta emitter, facilities receiving and administering the Sm-153 syringes as a unit dose should, in accordance with 10 CFR Part 35, record the administered dosage based on the activity specified by the preparer, Spectrum Pharmacy. A mathematical decay correction should be utilized if the actual time of administration differs substantially from the time for which the dosage has been prepared. Those facilities with Capintec dose calibrators could assay the syringe on the 273 setting to confirm the activity of Sm-153 in the syringe, but the recorded administered dosage should be the (decay corrected) activity specified by Spectrum Pharmacy. If the facility assay differs from Spectrum's specified activity by more than 10%, the dosage should not be administered and Spectrum should be contacted to resolve the discrepancy.

All appropriate staff at Spectrum Pharmacy and the clinical facility have been (will be) instructed regarding the above procedure.

Did Licensee Notify Patient or Guardian? Each surviving patient has or will be notified.

Information Provided to Patient, if any: A copy of this report is being provided to each surviving patient.

Samarium-153 Quadramet Dosage Error Data:

Date: 12-21-2001

Hospital Receiving Doses: Memorial Hospital South Bend, IN

Person Receiving Data: Dr. Nina Johnson\ Tracy King

Date of Prescription	Prescription Number	Act. Pres./ Dispensed	Syringe Error	Corrected Assay	Date of Injection	Time of Injection	Administered Activity	% Error
6/28/2000	718140	67 / 72.2	- 28.2%	51.84	6/28/2000	16:36	49.86	-25.6%
8/23/2000	735173	68 / 69	- 28.2%	49.54	8/23/2000	11:30	48.44	-28.8%
5/11/2001	816061	60 / 63.5	- 28.2%	45.59	5/11/2001	10:00	45.59	-24.0%
			- 28.2%					
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			- 28.2%					

SPECTRUM
PHARMACY, Inc.

December 24, 2001

NUCLEAR MEDICINE COLLEAGUES:

RE: ACCOUNT OF EVENTS LEADING TO CALIBRATION ERROR FOR Sm-153

The following is an explanation pertaining to the mistake made in the calibration and dispensing of prescriptions of Samarium-153 Quadramet. This error in calibration, by the pharmacy personnel, ultimately led to the apparent misadministrations within your hospital.

Samarium-153 Quadramet is an injectable radiopharmaceutical indicated for the palliative treatment of metastatic bone pain in terminal cancer patients. It is predominantly a Beta emitting isotope with some gamma emitting components.

Spectrum Pharmacy, Inc first began use of Sm-153 Quadramet on July 23, 1997. At this time a National Institute of Standards and Technology (NIST) traceable standard of Samarium-153 was obtained from DuPont Pharmaceuticals to facilitate calibration of Spectrum Pharmacy, Inc.'s Capintec dose calibrators. This NIST traceable vial was assayed in our dose calibrators to obtain a NIST traceable reference setting for dispensing Sm-153 Quadramet. A value of 170 was obtained and this value was used to calibrate all syringes containing Quadramet. On the morning of December 12, 2001 it came to the attention of one of the pharmacists that upon using a vial subtraction technique based on the manufacturer's assay, the assay of the vial and the assay of the syringe on the 170 calibration setting differed by a factor of approximately minus 25%. Spectrum Pharmacy, Inc. contacted both their health physics consultant, and the current manufacturer of Sm-153 Quadramet concerning this issue. The manufacturer (Berlex) stated that they did not believe that there was a significant difference in assays obtained whether the dose was in a vial or a plastic syringe. They also stated that there were no documented incidents of geometrical variation between syringes and vials for Sm-153. Our medical physics consultant believed that there may indeed be a difference in assays obtained between a glass vial and a plastic syringe due to the Beta emitting component of Samarium-153.

In order to determine the possible difference in assays, an NIST traceable standard was once again ordered from Bristol-Myer-Squibb Medical Imaging Division to obtain a syringe correction value. The Nuclear Regulatory Commission Region 3 office was notified of possible misadministrations of Sm-153 Quadramet doses on the morning of December 14, 2001. After reporting these possible incidents all hospitals involved were contacted by Spectrum Pharmacy, Inc. and instructed to call the Nuclear Regulatory Commission's Operations phone number to report the possible misadministrations. One hospital which received three doses in late 1998 was contacted on December 18th, 2001. The Nuclear Regulatory Commission issued a preliminary notification of the event on the morning of December 18, 2001. A copy was sent to Spectrum Pharmacy, Inc. as well as to all hospitals which were identified as to have received Sm-153 Quadramet doses from Spectrum Pharmacy, Inc.

1301 Mishawaka Blvd., Suite 100
Mishawaka, IN 46544
(219) 255-5072

On the afternoon of December 20, 2001 assays of the NIST traceable source were performed by Spectrum Pharmacy, Inc's Radiation Safety Officer, Scott Van Heesbeke R.Ph. The results of these assays were forwarded to Bob Anger our health physics consultant who was going to assist in the calculations for geometrical variation and differences of attenuation.

Upon evaluation of this data it was determined that there was indeed a difference in assays of Samarium-153 due to the density of the 10ml glass vial the product is calibrated and received from the manufacturer in, and the density of a plastic 3ml or 5ml Becton-Dickinson syringe which the Quadramet was assayed and dispensed for injection in. It was this attenuation difference that resulted in the calibration error due to using a syringe to dispense the Samarium-153 Quadramet. The data obtained from this calibration was used to obtain a secondary NIST traceable syringe dose calibrator reference setting of 273. From this point on Spectrum Pharmacy, Inc. has developed a protocol for assaying Sm-153 Quadramet patient injections which uses a manufacturer's assay vial subtraction technique and a secondary check of the assay using the 273 dose calibrator syringe reference setting.

Thank you for your time and assistance in resolving this matter.

Sincerely,

Scott Van Heesbeke R.Ph

Scott Van Heesbeke R.Ph.
Manager/RSO
Spectrum Pharmacy, Inc.

SPECTRUM
PHARMACY, Inc.

RE: ACTION PLAN FOR REPORTING PURPOSES
DATE: December 24, 2001

Dear Spectrum Pharmacy Colleagues:

On the afternoon of December 14, 2001 I, Scott VanHeesbeke of Spectrum Pharmacy spoke with the radiation safety officer of your hospital. I informed this individual that the possibility existed that prescriptions of Samarium-153 Quadramet were calibrated with 20% to 30% less activity than the amount indicated on the prescription and ordered by the physician. This error occurred due to a difference in the assay characteristics between a 10ml glass vial and a 3ml or 5ml plastic syringe. This was an unintentional mistake and we are very sorry that this error has occurred.

Please be aware that we are working with the Nuclear Regulatory Commission and our health physics consultant to make the reporting of these incidents, by your hospital, go as easily and accurately as possible. Attached you will find data specific to your hospital indicating the prescriptions dispensed, the date dispensed and the suspected dosage error as calculated by our health physics consultant. There is also an article from the Journal of Nuclear Medicine relating to the management of bone pain.

You are required to report to the Nuclear Regulatory Commission, in writing, within 15 days of initially discovering a misadministration (December 29, 2001). When corresponding with the Nuclear Regulatory Commission concerning this incident, you may consult the information included with this letter. This information lists the pertinent data you will need in putting together your report.

Additionally, our health physics consultant has prepared some guidelines that can be modified by each facility to prepare your written report to the NRC. In particular, the authorized users may want to expand the information in the effect on the patient section.

SUGGESTIONS FOR THE WRITTEN REPORT TO THE NRC

Brief description of the event:

Patients were administered an amount of Sm-153 that differed from the prescribed amount by more than 20%. (List each patient ID, not the patient's name, the ordered and the actual administered activities, as obtained from the Pharmacy)

1301 Milburn Blvd., Suite 100
Mishawaka, IN 46544
(219) 255-5072

Why it occurred

Unit patient dosages of Sm-153 were ordered from Spectrum Pharmacy, Mishawaka, IN, with a requested activity for a specified time. Spectrum Pharmacy filled these orders by withdrawing a calculated volume of Sm-153 into a 3 or 5 ml syringe from a 10 ml vial calibrated at 50mCi/ml at noon on Wednesday. The syringes were assayed in a Capintec ionization chamber dose calibrator on a setting of 170 , and the volume of the syringe was adjusted, if necessary, to produce an activity matching that requested by the ordering facility. The dose calibrator setting of 170 was determined on July 23, 1997, using a NIST traceable Sm-153 standard in a 10ml vial. During the period December 12-20, 2001, Spectrum Pharmacy determined that the 170 dial setting was appropriate only for the 10 ml glass vial, not for a syringe. Using another NIST traceable Sm-153 standard, Spectrum Pharmacy determined that the actual activity in a syringe is 28.2% less than the activity measured on the 170 setting.

Effect on the patient(s):

The Sm-153 was administered for palliation of bone pain. The effect, if any, of underdosing by 21 to 29% would presumably be a more than expected number of patients not experiencing relief from their symptoms.

Improvements needed, and actions taken, to prevent recurrence:

Spectrum Pharmacy, Mishawaka, has established that a Capintec dose calibrator setting of 170 is appropriate for the 10 ml of Sm-153 received from the manufacturer. It has also been determined that a setting of 273 is appropriate for Sm-153 in a 3 ml syringe. Both vial and syringe require no geometric correction factor over the range of 0.5 to 3 ml.

The Sm-153 dosages dispensed by Spectrum Pharmacy will be determined by a subtraction technique:

a. assay 10 ml vial on 170 setting
b. draw volume required into syringe, based on desired dosage and concentration of the Sm-153 solution
c. assay remainder in 10 ml vial on 170 setting
d. record dosage in syringe by subtracting remainder assay from the whole vial assay
e. confirm dosage by assaying the syringe on 273 setting

Since Sm-153 is primarily a beta emitter, facilities receiving and administering the Sm-153 syringes as a unit dose should, in accordance with 10 CFR Part 35, record the administered dosage based on the activity specified by the preparer, Spectrum Pharmacy. A mathematical decay correction should be utilized if the actual time of administration differs substantially from the time for which the dosage has been prepared. Those facilities with Capintec dose calibrators could assay the syringe on the 273 setting to confirm the activity of Sm-153 in the syringe, but the recorded administered dosage should be the (decay corrected) activity specified by Spectrum Pharmacy. If the facility assay differs from Spectrum's specified activity by more than 10%, the dosage should not be administered and Spectrum should be contacted to resolve the discrepancy.

All appropriate staff at Spectrum Pharmacy and the clinical facility have been (will be) instructed regarding the above procedures.

Were the patients notified? (If not, why not?)

This needs to be addressed for each of the patients identified in the "Brief description of the event".

I hope the information above and the provided enclosed data helps streamline and simplify your process and effort in the matter. Again, I am very sorry for the error in the calibration of the Sm-153 and promise you that corrective actions have already been implemented.

Sincerely,

Scott Van Heesbeke R Ph.

Scott Van Heesbeke R.Ph.
Manager/RSO
Spectrum Pharmacy, Inc.

Bone Pain Palliation with ^{85}Sr Therapy

Francesco Giammarile, Thomas Mognetti, Cyrille Blondet, Claude Desmonces and Paul Chauvot

Nuclear Medicine Department, Centre Léon Bérard, Lyon, France

The aim of this retrospective study was to evaluate the efficacy of ^{85}Sr in the palliation of metastatic bone pain. ^{85}Sr decays by electron capture with a gamma emission of 514 keV and associated x-ray emissions of 10–15 keV; physical half-life is 64 d. **Methods:** Between 1977 and 1992, 119 doses of ^{85}Sr chloride (mean activity 335 MBq [9 mCi]) were intravenously administered to 108 patients with hyperalgic generalized bone metastases from prostatic carcinoma (52 patients), breast carcinoma (41) or other cancers (15). Pain, performance status, blood and urinary excretion values were investigated during follow-up, and survival time was recorded. Strontium bone scans were obtained up to 8 wk after injection to document isotope biodistribution and to estimate absorbed doses. **Results:** At 12 wk, 72.2% of patients showed significant benefit from treatment, i.e., enhanced quality of life and pain relief; 49.1% became free of pain. These beneficial effects lasted from 1 to 36 mo (mean 4.3 mo). The best symptomatic improvement was seen in patients treated at an early stage of metastatic skeletal disease and in prostate cancer patients. No evidence of a significant dose-response relationship was found in the data analysis. The mean absorbed dose ratio of metastases to marrow was estimated at 8.2. We found no evidence that hematological toxicity was a major problem; however, all patients experienced a reduction in blood counts, especially in platelets. **Conclusion:** Systemic radionuclide therapy using ^{85}Sr is a feasible, effective and well-tolerated palliative treatment in patients with refractory bone pain. We attained at least the same response rate as that reported with bone-seeking β-emitting radionuclides such as ^{89}Sr. The patients who benefited the most from ^{85}Sr treatment were in an early stage of metastatic disease or had prostate cancer. Our clinical findings could not be linked to either the total injected activity of ^{85}Sr or the estimated absorbed dose delivered to metastases.

Key Words: ^{85}Sr; radionuclide therapy; bone pain palliation

J Nucl Med 1999; 40:585–590

The palliation of pain in patients with painful bone metastases is of primary importance in the clinical management of advanced cancer. Internal therapy with radionuclides, which concentrate at sites of increased bone turnover, is used to control pain and improve quality of life as an alternative to conventional therapies. The β-emitter ^{89}Sr was first used in 1941 for the palliation of pain from metastasized prostatic carcinoma (*1*). The effectiveness of ^{89}Sr therapy has been demonstrated by many researchers, suggesting that typically about 75% of patients have a clinic[illegible]efit (*2–8*). Although ^{32}P has been abandoned, because [illegible]ere bone marrow depletion, new agents like ^{186}Re-hy[illegible]ethylidene diphosphonate (HEDP), ^{153}Sm-ethylene di[illegible]tetramethylene phosphonate (EDTMP) or ^{117m}Sn-diet[illegible]etriamine pentaacetic acid (DTPA) have shown good [illegible] in human trials (*9–11*). In our institution, from 1977 t[illegible]2, ^{85}Sr was administered at therapeutic doses to patients [illegible]yperalgic generalized bone metastases. ^{85}Sr, formerly [illegible] for bone scanning, is a bone-seeking radionuclide [illegible]decays by electron capture, with a gamma emission of [illegible]-keV and a physical half-life of 64 d. The associated x-[illegible]missions of 10–15 keV allow an effective internal radi[illegible]apy, with a maximum dose delivered to the target with[illegible]ange of 10 mm (*12–17*). Although little is known about [illegible]losimetry in normal or pathological conditions, this [illegible]e has the advantage of documenting the metastatic e[illegible]on with a bone scan, which allows a macroscopic est[illegible]on of the absorbed dose to lesions (*12,18*).

The aim of this retrospective study was [illegible]aluate the efficacy of ^{85}Sr for the palliation of metastat[illegible]e pain.

MATERIALS AND METHODS

Patients

Between 1977 and 1992, 108 patients (62 male[illegible]emales; age 16–88 y, mean age 62.5 y) with hyperalgic [illegible]alized bone metastases (not satisfactorily relieved by drug t[illegible], including opiates) received a therapeutic dose of ^{85}Sr chl[illegible]1 patients with a good response after the first treatment [illegible]d a second dose because of recurrence of pain 3–9 mo late[illegible]e a total of 119 doses (mean dose 335 MBq, 9 mCi). The [illegible]ary sites of tumor were prostate (52 patients, mean age 69.[illegible]oses, mean activity 335 MBq, 9 mCi), breast (41 patients, me[illegible]: 56.2 y; 43 doses, mean activity 355 MBq, 9.5 mCi) or othe[illegible] patients, 10 males and 5 females, mean age 57.8 y, 16 do[illegible]ean activity 290 MBq, 7.8 mCi) (Table 1). Only patients [illegible]erformance status ≤ 2, a life expectancy of at least 3 mo and [illegible]eptable blood counts (leukocytes > 2.5×10^9/L; range 3.2–13.2[illegible]^9/L, mean 5.3 × 10^9/L; thrombocytes > 75×10^9/L; range [illegible]–730 × 10^9/L, mean 189 × 10^9/L) were eligible (Table 2). To do[illegible] the extent of the metastatic disease, all patients underwent a [illegible]-methylene diphosphonate (MDP) bone scan a few days befo[illegible] therapeutic injection of ^{85}Sr. We counted 8 cases of paucifoc[illegible]tension (<5 lesions), 27 of plurifocal extension (5–10 sites), 4 of diffuse metastatic involvement (more than 10 sites) (Table 3). Before radionuclide therapy, all patients had received [illegible] therapy or hormonal therapy, plus radiotherapy on painful [illegible]

Received Mar. 24, 1998; revision accepted Oct. 3, 1998.

For correspondence or reprints contact: Francesco Giammarile, MD, Centre Léon Bérard, Service de Medecine Nucléaire, 28, rue Laënnec, F-69373 Lyon cedex 08, France.

TABLE 1
Patient Characteristics

Site	Age (y)	No. of patients	Dose (MBq)
Prostate	54–89 (median 68)	56*	740 (370–830)
Breast	34–78 (mean 56.7)	41†	555 (370–830)
Others	16–78 (mean 57.8)	15 (10*, 5†)	740 (370–780)
Total	16–88 (mean 62.5)	108 (62*, 46†)	780 (345–830)

*Male.
†Female.

Dosimetry

Because of the hematological toxicity of the ...nent, the standard dose of 370 MBq (10 mCi) was reduc... ...cally in cases of high risk of bone marrow depletion (ad... ...ge, recent chemo- or radiotherapies, large extent of the meta... ...isease on bone scans). Conversely, the dose was increased ... ...of severe pain or if the metastatic extension to bone was l... ...efore, the mean activity administered was 555 MBq, but t... ...ge varied from 45 to 740 MBq (1.2–20 mCi) (Table 1).

Follow-up

To avoid environmental contamination after th... ...ection, all patients were admitted to hospital isolation facilit... ...t least 7 d (mean 10 d), until radiation doses returned to the ... ...ted levels (25 μSv/h at a distance of 1 m from the body). Dur... ...spitaliza- tion, urine was collected and its activity measured ... ...ium bone scans, obtained up to 8 wk after injection, allowed ... ...mentation of isotope biodistribution and estimation of ab... ...oses. For each patient, a clinical follow-up was performed at ... ...nd 12 wk. A blood count was also obtained. Any modificati... ...one pain, mobility and use of pain medication was recorded ... ...relief was evaluated subjectively by the patient and ob... ...by the reduction of the analgesic dose and the change ... ...formance status. The response to treatment was defined a... ...ete (com- plete pain relief, a decrease in performance statu... ...ss it was already 0] and at least a 50% decrease in opiate ... during at least 4 mo, unless patient died sooner than 4 mo... persisting efficient pain control), partial (significant impro... ...t of pain control during at least 2 mo) or none (all others). An... ...uration of the remission was recorded.

TABLE 2
Performance Status

Performance status (WHO)	No. of ... (%)
0	13 (1...
1	68 (6...
2	38 (3...

WHO = World Health Organization.

TABLE 3
Metastatic Extent to Bone

Bone metastatic ... by ... Tc ... scan	No. of cases (%)
5	8 (6.7)
5–10	27 (22.7)
>10	84 (31.9)

Statistics

A statistical program was used for calculations of medians, ranges and the analysis of variance. χ^2 test was also used where specified. P value ≤ 0.05 was considered as statistically significant. When using χ^2 test, partial response and complete response were considered as one group. No valid control group could be set up because most eligible patients in our institution received ^{85}Sr treatment.

RESULTS

Clinical Results

The quality of the post-therapeutic ^{85}Sr bone scans was mostly acceptable (Fig. 1). Whole-body distribution of ^{85}Sr

FIGURE 1. Images of 55-y-old man with metastatic prostatic carcinoma were obtained 14 d after intravenous injection of 445 MBq (12 mCi) ^{85}Sr, using large field-of-view gamma camera with high-energy collimator rated to 514 keV. Anterior and posterior whole body images show multiple focal areas of increased uptake at metastatic sites.

was similar to that of the MDP. Overall, pain relief and relief 1 wk after the first ^{89}Sr administration in all 108 patients (78.2%) of 58 patients (96.6%) of the same sites were pain free and 28 patients (23.1%) had partial pain relief. After the second dose, only 6 of 11 patients (54.5%) showed some benefit from treatment (Table 4). A flare response was observed in 4 patients (3.7%) between the second and the fourth day. Symptomatic improvement, when it did occur, usually occurred between the fourth and the eighth day. A couple of patients reported some relief as soon as the following day (this may partly account for a decrease in activity of patients confined in their room). Beneficial effects lasted from 1 to 36 mo with a mean of 4.3 mo (4.7 mo in cases of complete response and 3.4 mo in cases of partial response).

TABLE 4
Clinical Results

Site of primary tumor	Pain relief			
	None	Partial	Complete	Total
Prostate				
Cases (%)	14 (23.3)	14 (23.3)	32 (53.3)	60 (100)
Patients (%)	10 (19.2)	13 (25)	29 (55.8)	52 (100)
Mean activity injected (MBq)	290	330	355	335
Mean duration (mo)*	—	4.2	4.7	4.6
Mean survival (mo)†	3.5	9.5	10.2	8.5
Mean survival (mo)‡	4.2	9.5	10.7	9.1
Breast				
Cases (%)	13 (30.2)	8 (18.6)	22 (51.2)	43 (100)
Patients (%)	13 (31.7)	8 (19.5)	20 (48.8)	41 (100)
Mean activity injected (MBq)	415	315	335	355
Mean duration (mo)*	—	2.9	5.0	4.4
Mean survival (mo)†	2.4	5.3	10.1	6.9
Mean survival (mo)‡	2.6	5.3	10.1	7.2
Other				
Cases (%)	8 (50)	4 (25)	4 (25)	16 (100)
Patients (%)	7 (46.7)	4 (26.7)	4 (26.7)	15 (100)
Mean activity injected (MBq)	285	370	210	290
Mean duration (mo)*	—	1.8	3.3	2.6
Mean survival (mo)†	2.0	6.8	4.8	3.9
Mean survival (mo)‡	2.6	6.8	6.0	4.9
Total				
Cases (%)	35 (29.4)	26 (21.9)	58 (48.8)	119 (100)
Patients (%)	30 (27.8)	25 (23.1)	53 (49.1)	108 (100)
Mean activity injected (MBq)	335	330	335	335
Mean duration (mo)*	—	3.4	4.7	4.3
Mean survival (mo)†	2.8	7.8	9.8	7.3
Mean survival (mo)‡	3.3	7.8	10.2	7.9

*Mean duration of the pain relief in cases of partial or complete response.
†Mean survival including those who died in the first 4 wk.
‡Mean survival excluding patients who died in the first 4 wk.

TABLE 5
Results Depending on the Performance Status and on the Extent of Metastatic Disease

Performance status	Pain relief		
	None	Partial	Complete
0	3 (23.1)	1 (7.7)	9 (69.2)
1	15 (17.6)	14 (20.6)	42 (61.7)
2	20 (52.6)	11 (28.9)	7 (18.4)
Total	35 (29.4)	26 (21.9)	58 (48.8)
Extent of metastatic disease			
5 metastatic sites	2 (25)	1 (12.5)	5 (62.5)
5–10 metastatic sites	2 (7.4)	5 (18.5)	20 (74.1)
>10 metastatic sites	31 (36.9)	20 (23.8)	33 (39.3)
Total	35 (29.4)	26 (21.9)	58 (48.8)

With regard to the site of primary tumor, the higher symptomatic improvement was obtained in patients with prostate cancer (76.6% of pain relief, with mean response of 4.6 mo). Furthermore, the survival was longer in patients with meaningful clinical response, especially when excluding patients who died in the first 4 wk after therapy, but only in prostate ($P < 0.05$) and breast cancers ($P < 0.01$); no significant difference in survival was shown in other cancers, whether one includes or excludes patients who died in the first 4 wk. A correlation between the performance status and the response was seen: The better results were obtained in patients with good general condition (χ^2 test, $P < 0.01$) (Table 5). Another correlation between the extent of bone metastases and the response was seen: The better results were obtained in patients with fewer metastases on the ^{85}Sr bone scan (χ^2 test, $P < 0.01$) (Table 5).

For prostate cancer patients, the clinical results may seem slightly related to the injected activity (highest mean activity and best results), but a global data analysis showed no evidence of a significant dose-response relationship overall.

Dosimetric Results

Theoretically, the absorbed dose delivered to bone (D) at infinite time, during ^{85}Sr radiotherapy, is given by:

$$D = k \times (A - U),$$

where A is the administered activity and U is the urinary excretion. For a simple estimation of the absorbed dose, we considered the cumulative urinary excretion of ^{85}Sr during only the first 7 d after injection. Therefore, we assumed, according to total-body strontium retention studies in normal subjects previously performed and using the Interna-

tional Commission on Radiation Protection models for bone density, that is, 0.65 cGy/MBq for bone surface and marrow and 1.3 cGy/MBq for bone volume (22). In pathological conditions, the ratios for normal D_n and pathological D_p compartments are not equivalent and one must take into account the metastatic extension M that has a proper relative uptake R. Thus, if we imagine a homogeneous distribution of the radioisotope

$$D = M \times D_p + (1 - M) \times D_n \quad \text{and} \quad D_p = R \times D_n,$$

knowing U (urine samples, M and R evaluated from the ^{87}Sr bone scan), it is possible to estimate the absorbed dose to normal and pathological compartments delivered by the administered activity A at infinite time.

In this work, the estimation was impossible to make in 27 of 119 cases, because of a failure to collect the urine effectively or the bad quality of the images (Table 6). Usually, the urinary excretion of ^{87}Sr was important mainly in the first 2 d after therapeutic administration, representing about 75% of the total activity in urine collected during hospitalization. The macroscopic dose estimation suggested that the absorbed dose by normal bone marrow rarely exceeded 70 cGy for all of the patients. The absorbed dose ratio of metastatic bone to marrow ranged from a low of 3 to a high of 15, with a mean of 8.2. Although the estimated doses delivered to lesions seemed higher in cases of complete response (mean 630 cGy, with a ratio of absorbed dose of 1.81 cGy/MBq [67 cGy/mCi]), especially in prostate cancers, this has not been proved statistically significant.

Hematological Results

In a significant number of cases, these data were sparse. A reduction in leukocyte and thrombocyte levels was observed in most patients, with a mean time to reach the nadir of about 6 wk. The mean reduction at nadir was about 30% for leukocytes and 40% for thrombocytes (Table 7). The toxicity of the treatment seemed higher with bone marrow depletion as a consequence of either previous treatments or metastatic marrow involvement. Transfusion was necessary in 24 patients, with no significant relation to dose, but 23 of them had already needed transfusions before ^{87}Sr therapy. No connection was observed between the reduction of blood counts and the extent of bone metastases. One patient with significant bone marrow involvement had a fatal myelodepression in the fourth month. In another patient, an acute myeloid leukemia was reported 11 mo after treatment.

TABLE 6
Dosimetric Results

Site of primary tumor	Pain relief			
	None	Partial	Complete	Total
Prostate				
Cases (%)	5 (17.9)	11 (39.3)	27 (58.7)	46 (100)
Mean activity (MBq)	305	340	370	350
Urinary excretion*	22.0	20.1	17.5	18.9
Dose to metastases (cGy)†	542	548	674	621
Dose to marrow (cGy)‡	69	70	72	71
Dose ratio (cGy/MBq)§	1.78	1.61	1.82	1.77
Tumor ratio¶	7.86	7.83	9.36	8.74
Breast				
Cases (%)	11 (33.3)	6 (18.2)	16 (48.5)	33 (100)
Mean activity (MBq)	415	325	335	360
Urinary excretion*	35.8	33.5	24.6	30.0
Dose to metastases (cGy)†	493	555	574	544
Dose to marrow (cGy)‡	70	75	70	71
Dose ratio (cGy/MBq)§	1.19	1.71	1.71	1.51
Tumor ratio¶	7.04	7.40	8.20	7.66
Other				
Cases (%)	6 (46.2)	4 (30.8)	3 (58.7)	13 (100)
Mean activity (MBq)	305	370	220	305
Urinary excretion*	26.1	22.3	16.3	22.7
Dose to metastases (cGy)†	491	555	534	520
Dose to marrow (cGy)‡	62	74	63	66
Dose ratio (cGy/MBq)§	1.61	1.50	2.43	1.70
Tumor ratio¶	7.92	7.50	8.48	7.90
Total				
Cases (%)	25 (27.2)	21 (23.9)	46 (50)	92 (100)
Mean activity (MBq)	355	340	350	350
Urinary excretion*	29.0	24.3	19.9	23.4
Dose to metastases (cGy)†	508	551	630	579
Dose to marrow (cGy)‡	68	72	71	70
Dose ratio (cGy/MBq)§	1.44	1.62	1.81	1.66
Tumor ratio¶	7.49	7.65	8.89	8.24

*Cumulated after 7 d, expressed as percentage of the administered activity.

†Mean estimated dose to metastases.

‡Mean estimated dose to normal bone marrow (the estimated dose to normal bone is four times this value (12).

§Mean ratio between dose to metastases and activity.

¶Mean ratio between dose to metastases and normal bone marrow.

DISCUSSION

Systemic radionuclide therapy is an optimal choice in the management of intractable metastatic bone pain. However, despite many large-scale studies, the choice of the optimal radiopharmaceutical is still under discussion. Among the potential radionuclides, ^{89}Sr and ^{153}Sm EDTMP are approved for metastatic pain palliation by American, French and other European regulatory authorities, and new agents

TABLE 7

Hematological T[illegible] 6 Weeks After Therapy

Toxicity	[illegible]	[illegible]
Grade I	[illegible]	75
No. of cases (%)	53 (45)	42 (35)
Grade II	2.0–2.9	50–74.9
No. of cases (%)	18 (15)	30 (25)
Grade III	1.0–1.9	25–49.9
No. of cases (%)	12 (10)	24 (20)
Grade IV	< 1.0	< 25
No. of cases (%)	1 (1)	1 (1)

like ^{186}Re-HEDP and ^{117m}Sn-DTPA have shown good results (*4–11*).

We wanted to review our experience with ^{85}Sr, used from 1977 to 1992 at therapeutic doses, in patients with hyperalgic generalized bone metastases.

^{85}Sr decays by electron capture with a gamma emission of 514 keV, thus allowing imaging. Obviously, ^{99m}Tc-MDP, which presents better physical (radioprotection and imaging) and logistic (cost, availability) characteristics, is the radiopharmaceutical of choice for diagnostic purposes. However, because of the associated x-ray emissions of 10–15 keV, ^{85}Sr provides an effective internal radiotherapy, with a maximum dose delivered to target within a range of 10 mm (in water and soft tissues), which is similar to that of ^{89}Sr (*12–17*). The standard dose of 370 MBq (10 mCi) ^{85}Sr was reduced empirically in cases of high risk of bone marrow depletion (i.e., advanced age, recent treatments) and increased if the bone pain was high or if metastatic extension to bone was low (estimated by ^{99m}Tc-MDP bone scan).

In this study, the global hematological toxicity of the treatment was low, the most significant factor being a decrease in platelet counts that was partially restored a few months later. However, 1 patient with significant bone marrow involvement had a fatal myelodepression in the fourth month. This patient, who had not undergone previous chemotherapy, was 77 y old and received an average dose to normal bone marrow of 49 cGy. We believe that the age of the patient and the extent of marrow involvement can explain the aplasia. One case of acute myeloid leukemia was reported after 11 mo of treatment, thus no causal relationship with the therapy can be clearly established.

Although no connection was observed between the reduction of blood counts and the extent of bone metastases, the former was incompletely documented and the latter was quoted only according to the number of sites as few, many or diffuse. Because the extent of bone metastases was not pivotal in this study, we did not expand on it as did de Klerk et al. (*19*).

Clinical results demonstrated that ^{85}Sr is effective in the great majority of patients, even when conventional treatments have failed. At 12 wk, 72.2% of patients had significant benefit from treatment in terms of enhanced quality of life and subjective pain relief: 49.1% became free [illegible] pain. [illegible] adverse effects lasted [illegible] mean of [illegible] mo. Therefore, we [illegible] response rate as that reported with [illegible] [illegible] slightly longer [illegible] clinical response when excluding [illegible] first [illegible] after therapy, but the [illegible] prostate [illegible] and breast ca[illegible] [illegible] at least the same [illegible] Further, [illegible] with metastatic [illegible] who died [illegible] the [illegible] significant [illegible] in [illegible].

From the analysis of the results [illegible] that the clinical response was [illegible] correlated with patients' general [illegible] bone involvement, those patients [illegible] the best improvement, especially in [illegible] the extent of bone metastases on [illegible] to represent a reliable prognostic [illegible] of the treatment, as for the other ra[illegible] [illegible] is an advantage in treating metast[illegible] early stage (*5–11*). This finding was [illegible] [illegible] some indication [illegible] related but was [illegible] and metastatic [illegible] [illegible] stages showed [illegible] [illegible] cancer. Because [illegible] scan was shown [illegible] of the efficiency [illegible] [illegible] pharmaceuticals, there [illegible] skeletal disease at an [illegible] reported by another author (*20*).

It is important to notice that [illegible] 11 patients who received a second dose of ^{85}Sr after [illegible] palliation effect of the first one ended, the clinical res[illegible] was generally less significant than the one seen with [illegible] dose.

Because a simple evaluation of [illegible] results on the basis of the total administered activity seem[illegible] unreliable, we tried to evaluate the ^{85}Sr retention in the le[illegible] A precise dosimetric evaluation presents logistic pr[illegible] (especially important with 119 cases) and question[illegible] results because of the nonuniformity of the dose distr[illegible] within the lesions (heterogeneity of the material and [illegible] distribution of the radionuclide (*31*). The aim of th[illegible] study of ^{85}Sr therapy efficiency was essentially clinical. [illegible] fore, we performed a macroscopic dose estimation by [illegible] [illegible] ring the cumulative urinary excretion of ^{85}Sr during [illegible] hospitalization and the patterns of uptake of the lesions [illegible] bone scans. Because ^{85}Sr uptake is attributed to an [illegible] [illegible] mechanism with calcium in the bone mineral ma[illegible] body retention, evaluated by urinary excretion, is du[illegible] the avid uptake of the radionuclide in lesion sites. [illegible] same reason, the extension and the metabolic a[illegible] of the metastases, shown on ^{85}Sr bone scan, positi[illegible] influences the absorbed dose delivered to the lesions. T[illegible] [illegible] iting factors in these dose estimations are the poor re[illegible] of the ^{85}Sr bone scan and the short duration of the [illegible] collection. However, these dosimetric estimations sho[illegible] that the differences in pain relief could not be linked [illegible] statistically significant way to the injected activity or [illegible] dose delivered to the metastases.

With our assumptions, we ca[illegible] [illegible] ted that the delivered dose to metastases at infinite [illegible] ranged from 674 cGy (complete pain relief in prostate [illegible] [illegible] er patients) to 491 cGy (no response in other cancer pat[illegible] with a mean value of 579 cGy. The estimated absorbe[illegible] [illegible] es are sufficiently large to expect a therapeutic benefit. [illegible] to red marrow were smaller by a factor of about 8. [illegible] values are similar to those published with ^{89}Sr (*5*, [illegible] [illegible] versely, our values of cumulative ^{85}Sr retention, 7 d af[illegible] [illegible] therapeutic injection,

seemed higher than in other studies, probably because of a larger metastatic bone tumor burden in our patients (2,3,5).

CONCLUSION

Systemic radionuclide therapy with ^{85}Sr is a feasible, effective and well-tolerated palliative treatment in patients with refractory bone pain. Almost all patients received a benefit, lasting up to 3 years, in cancer with very few serious side effects. This therapy is especially effective in patients with prostate cancer. The best results were obtained when patients received the treatment in an early stage of metastatic disease. This has also been shown with ^{89}Sr and contrasts with the usual indication for palliative radionuclide therapy. Response was related neither to injected activity nor estimated dose. A major problem of ^{85}Sr therapy is related to the gamma emission of the isotope and to radioprotection problems. However, in this retrospective study, we attained at least the same response rate as that reported with bone-seeking β-emitting radionuclides. Thus the use of ^{85}Sr for therapeutic purposes should be reconsidered.

A limitation of this study is the absence of a control group. These results would theoretically warrant a prospective study to evaluate ^{85}Sr versus another bone seeking radionuclide, but the radioprotection problem is such that it is unlikely it will be done in the foreseeable future.

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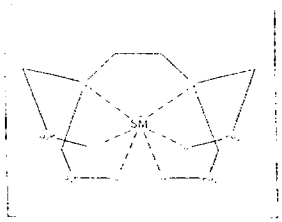
QUADRAMET®

(Samarium Sm 153 Lexidronam Injection)

Therapeutic - For Intravenous Administration

DESCRIPTION: [illegible] is a radiopharmaceutical [illegible] for intravenous administration. [illegible] is a complex of samarium-153 and ethylenediaminetetramethylene phosphonic acid (EDTMP). [illegible] is supplied as a sterile, nonpyrogenic, clear, colorless to slightly yellow solution [illegible] for intravenous administration. [illegible] contains 50 mg Sm/mL (1.3 mCi/mL) [illegible] 64 mg Cu/mL EDTMP, [illegible] 5 mg/mL benzyl alcohol as a preservative, [illegible] sodium and 1850 ± 185 MBq/mL (50 ± 5 mCi/mL) samarium-153 at calibration [illegible]

Chemical formula of samarium-153 lexidronam: [illegible]



The chemical formula is $^{153}Sm^{+3}$ [illegible] and the sodium [illegible] is 153.9 Daltons. The tetrasodium form is 690.

The pH of the solution is 7.0 to 8.5.

Each vial is supplied frozen in a single-dose glass vial containing [illegible] with a radioactivity of [illegible] MBq (100 mCi) or 3 mL with 5550 MBq (150 mCi) of samarium-153 at calibration.

Physical Characteristics: Samarium-153 is produced in a high-flux nuclear reactor by neutron activation of isotopically enriched samarium Sm-152 oxide ($^{152}Sm_2O_3$). It undergoes beta particle and a gamma photon, and has a physical half-life of 46.3 hours (1.93 days). Samarium-153 has an average and maximum beta particle ranges in water of 0.8 mm and 3 mm, respectively. The energy of each emissions of samarium-153 are shown in Table 1.

TABLE 1 - SAMARIUM-153
PRINCIPAL RADIATION EMISSION DATA

	Radiation Energy (keV)*	Abundance
Beta	640	30%
Beta	710	50%
Beta	810	20%
Gamma	103	29%

*Maximum energies are listed for the beta emissions. The average beta emission energy is 225 keV.

External Radiation: The specific gamma ray constant for samarium-153 is [illegible] 0.30 R/mCi/hr at 1 cm or [illegible]x10^{-3} mSv/MBq/hr at 1 meter. The half value thickness of lead for samarium-153 is approximately 0.16 mm. The use of 1 mm lead will decrease the radiation exposure by a factor of approximately 1,000. Quadramet should be stored in a lead-shielded container and frozen until use.

Decay factors to be applied to the stated value for radioactivity at calibration at calibration are given in Table 2. All radioactivity is calibrated to the reference date and time on the vial.

TABLE 2 - SAMARIUM-153
PHYSICAL DECAY CHART, HALF-LIFE 46.3 HOURS
(1.93 DAYS)

Time (hour)*	Factor	Time (hour)*	Factor
-48.0	2.05	[illegible]	0.99
-36.0	1.71	[illegible]	0.97
-24.0	1.43	[illegible]	0.96
-20.0	1.35	[illegible]	0.95
-16.0	1.27	[illegible]	0.91
-12.0	1.20	[illegible]	0.89
-8.0	1.13	[illegible]	0.84
-6.0	1.09	[illegible]	0.80
-4.0	1.06	[illegible]	0.74
-3.0	1.05	[illegible]	0.70
-2.0	1.03	[illegible]	0.63
-1.0	1.02	[illegible]	0.57

*Hours before (-) or after (+) calibration

CLINICAL PHARMACOLOGY: [illegible] differ [illegible] in terms of bone localization with hydroxyapatite [illegible] bone scanning [illegible] Quadramet [illegible] than [illegible]

Distribution: [illegible]

Skeletal Uptake: [illegible] 1 to 3 mCi/kg the ^{153}Sm EDTMP taken up by bone [illegible]

Metabolism: [illegible] is excreted as an intact [illegible] The stability of the Sm-153 and the molecule of the EDTMP as shown by an analysis of [illegible] in patients in Phase 3 studies [illegible] Samarium Sm-153 EDTMP. Metabolic products of Sm-153 EDTMP were not detected in the urine.

Elimination: [illegible] detected in the whole body profile and dose 2 were corrected for attenuation decay. The [illegible] relatively through the urine is expressed as the [illegible] The whole body retention [illegible] The simple reciprocal of the cumulated urine activity [illegible] plasma Sm-153.

[illegible] of radioactivity from the blood is described by exponential kinetics after administration [illegible] patients (10 men, 9 women) with a variety of primary cancers that were metastatic to bone. Over the first 30 minutes, the radioactivity [illegible] in the blood decreased to 15% (±6%) of the injected dose with a t 1/2 of 5.5 minutes (1.1 SD). After 30 minutes, the radioactivity cleared from the blood more slowly with a t 1/2 of 66.4 hours (±9.1 SD). Less than 1% of the dose injected remained in the blood 5 hours after injection.

Unchelated Samarium Sm-153 EDTMP [illegible] was excreted in the urine after intravenous injection. During the first 6 hours, 34.5% (±15.5%) was excreted. Overall, the greater the number of metastatic lesions, the more radioactivity was excreted.

Gender Differences: Gender did not affect the samarium Sm-153 EDTMP blood pharmacokinetics, the cumulative % of radioactivity excreted in urine, or the % radioactivity retained in the skeleton when the number of metastatic lesions is taken into account.

Special Populations

Elderly: The pharmacokinetics of samarium Sm-153 EDTMP did not change with age as seen from comparisons of values from people in the age range 22 to 64 compared to the range 65 to 86 years.

Hepatic Insufficiency: Samarium Sm-153 EDTMP [illegible] scans in 5 patients with metastatic bone disease showed [illegible] accumulation of activity in the liver or the intestine; this suggests that hepatobiliary excretion did not occur.

Renal Insufficiency: Patients with renal insufficiency have not been studied.

Drug/Drug Interaction

Drug-drug interaction studies have not been studied.

Pharmacodynamics

The beta particles of ^{153}Sm EDTMP travel an average of 3.1 mm in soft tissue and 1.7 mm in bone. In [illegible] trials of 78 patients with metastatic bone lesions who had 13 specific bone scan sites evaluated, the presence or absence of ^{153}Sm-EDTMP uptake is similar to the presence or absence of ^{99m}Tc diphosphonate uptake in [illegible] range 67 to 96% agreement depending upon the blinded reader and the site of the body. Whether the amount of ^{153}Sm EDTMP uptake varies with the size of the lesion or to the presence of osteolytic components has not been studied. The clinical benefit of Sm-153-EDTMP in patients with osteolytic lesions is not known. The relationship of different tumor cell types to clinical response has not been studied.

CLINICAL TRIALS

Overall safety was evaluated in 580 patients (see Adverse Events Section for demographic description). Of these patients, 270 (244 men, 26 women) were studied in two randomized, blinded, placebo controlled clinical trials. These patients had a mean age of 67 and a range 22 to 87 years. Eligible patients had painful metastatic bone lesions that had failed other treatments, had at least a 6 month expected survival and had a positive radionuclide bone scan. Routine x-rays to evaluate the metastatic lesions were not part of the protocol.

In study A, 118 patients were randomized to receive 0.5 mCi/kg Quadramet, 1.0 mCi/kg Quadramet, or a placebo intravenous injection. In study B, 152 patients were randomized to receive either 1.0 mCi/kg Quadramet or a placebo intravenous injection. Both studies were double blind over a 4 week period. Patients scored their daily pain intensity on a 11-point analogue scale rated from 0 (no or low pain) to 10 (excruciating pain). The area under the pain curve (AUPC) was obtained by integrating the daily pain scores by week. Opioid analgesic use was recorded daily and averaged over each week and expressed as oral morphine milligram equivalents.

Of the 270 patients studied, 232 (86%) had prostate cancer and 38 (14%) had other primary cancers. In study A, 90 (88%) of the patients had prostate cancer and 38 (32%) had a variety of other primary cancers. In study B, all (100%) patients had prostate cancer.

The results of the patients' AUPC scores are shown in Table 3. In both trials for each of the 4 weeks of study, the mean AUPC scores decreased in patients who received Quadramet (1.0 mCi/kg). In study A, baseline AUPC's [illegible] baseline was significantly different in Quadramet 1.0 mCi/kg and placebo groups at weeks 3 and 4. In study B, pain (the AUPC) decrease from baseline was significantly different in [illegible] 1.0 mCi/kg and placebo groups at weeks 2, 3, and 4.

Table 3: COMPARISON OF WEEKLY PAIN SCORES (a) AFTER QUADRAMET 1.0mCi/kg or PLACEBO IV [Intent to Treat]

[illegible]

Table 4: COMPARISON OF WEEKLY MEAN ANALGESIC USE (a) BETWEEN QUADRAMET 1.0 mCi/kg AND PLACEBO GROUPS [Intent to Treat]

	STUDY A (n = 73) (b)		STUDY B (n = 149) (c)	
WEEK	Placebo N=36	1.0 mCi/kg N=37	Placebo N=50	1.0 mCi/kg N=99
Baseline	93.5 (154.0)(a)	127.1 (189.9)	78.4 (83.1)	90.5 (106.0)
1	106.8 (173.8)	125.7 (192.6)	84.5 (91.1)	93.5 (105.1)
2	127.1 (238.4)	144.8 (276.7)	85.6 (90.9)	82.9 (112.9)
3	133.9 (254.0)	146.6 (278.2)	100.1 (119.4)	79.6 (113.2)*
4	135.6 (222.0)	135.1 (274.0)	106.3 (161.0)	76.8 (132.3)*

(a) Mean Analgesic Use (SD) is in morphine equivalent units (I = Ionte

(b) Excludes 5 patients with missing baseline or with extreme values and an 0.5 mCi Quadramet. Quadram of 0.5 mCi/kg can not be distinguished from placebo.

(c) Excludes 2 patients with missing baseline values

(*) Statistically significant difference in change from baseline in comparison to placebo

In both studies, the numbers of patients who experienced any decrease in AUPC score without any increase in analgesic use at weeks 3 and 4 were also evaluated. In study A, this occurred in 20/37 (54%) of the patients who received Quadramet 1.0 mCi/kg and 9/36 (25%) of the placebo treated patients. In study B, this occurred in 49/100 (49%) of the Quadramet treated patients and 11/51 (22%) of the placebo treated patients.

INDICATIONS: Quadramet is indicated for relief of pain in patients with confirmed osteoblastic metastatic bone lesions that enhance on radionuclide bone scan.

CONTRAINDICATIONS: Quadramet is contraindicated in patients who have known hypersensitivity to EDTMP or similar phosphonate compounds.

WARNINGS: Quadramet Caused Bone Marrow Suppression. In clinical trials, while platelet counts and platelet counts decreased to a nadir of approximately 40% to 50% of baseline at 123 (95%) of patients within 3 to 5 weeks after Quadramet and tended to return to pretreatment levels by 8 weeks. The grade of marrow toxicity is shown in Table 5 below.

Table 5: NUMBER AND PERCENT OF PATIENTS WHO EXPERIENCED MARROW TOXICITY IN CLINICAL TRIALS OF QUADRAMET

	Hemoglobin		Leucocytes		Platelets	
Toxicity Grade*	Placebo N = 85	1.0 mCi/kg N = 185	Placebo N = 85	1.0 mCi/kg N = 184	Placebo N = 85	1.0 mCi/kg N = 185
0-2	78 (92%)	162 (88%)	85 (100%)	169 (92%)	85 (100%)	175 (95%)
3	6 (7%)	20 (11%)	0 (0%)	15 (8%)	0 (0%)	10 (5%)
4	1 (1%)	3 (2%)	0 (0%)	0 (0%)	0 (0%)	2 (1%)

* Toxicity Grade based upon National Cancer Institute Criteria, normal levels are Hemoglobin >10g/dl, Leucocyte ≥4.0 x 10^3/µL, and Platelets ≥150,000/µl.

Before Quadramet is administered, consideration should be given to the patient's current clinical and hematologic status and bone marrow response history to treatment with myelotoxic agents. Metastatic prostate and other cancers can be associated with disseminated intravascular coagulation (DIC); caution should be exercised in treating cancer patients whose platelet counts fall out of the clinical or laboratory findings suggesting DIC. Because of the cumulative toxic effect on bone marrow, Quadramet should not be given concomitantly with chemotherapy or external beam radiation therapy unless the benefit outweighs the risks. Quadramet should not be given to patients with evidence of compromised bone marrow reserve from previous therapy or disease considered [illegible] unless the potential benefits of the treatment outweigh the risks. Blood counts should be monitored weekly for at least 8 weeks, or until recovery of adequate bone marrow function.

PRECAUTIONS: [illegible]

Because [illegible] Dysplasia [illegible] to preclude the urinary bladder [illegible] appropriate [illegible] and catheterization of the bladder immediately following administration of Quadramet should be [illegible] patients with a history [illegible] urinary tract disease or urinary incontinence.

Bone [illegible] should be used with caution in patients with compromised bone marrow reserves. See Warnings.

Skeletal [illegible] spinal cord compression usually occurs in patients with known disease of the cervical thoracic [illegible] lumbar spine. In clinical studies of Quadramet, spinal cord compression occurred in 7% of patients who received placebo and in 6.3% of patients who received 1.0 mCi/kg Quadramet. Quadramet is not indicated for treatment of spinal cord compression. Quadramet administration for pain relief or metastatic bone lesions does not prevent the development of spinal cord compression. When there is clinical suspicion of spinal cord compression, appropriate diagnostic and therapeutic measures must be taken immediately to avoid permanent disability.

Radiopharmaceutical agents 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.

Quadramet, like other radioactive drugs must be handled with care, and appropriate safety measures must be taken to minimize radiation exposure of clinical personnel and [illegible] the patient environment.

Special precautions, such as bladder catheterization, should be taken with incontinent patients to minimize the risk of radioactive contamination of clothing, bed linen, and the patient's environment. Urinary excretion of radioactivity occurs over about 12 hours, with 35% occurring during the first 6 hours). Studies have not been done on the use of Quadramet in patients with renal impairment.

INFORMATION FOR PATIENTS Patients who receive Quadramet should be advised that for several hours following administration radioactivity will be present in excreted urine. To help protect themselves and others in their environment, precautions need to be taken for 12 hours following administration. Whenever possible, a toilet should be used, rather than a urinal, and the toilet should be flushed several times after each use. Spilled urine should be cleaned up completely and the area should wash their hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately, or stored for 1 to 2 weeks to allow for decay of the Sm-153.

Some patients have reported a transient increase in bone pain shortly after injection (flare reaction). This is usually mild and self-limiting and occurs within 72 hours of injection. Such reactions are usually responsive to analgesics.

Patients who respond to Quadramet might begin to notice the onset of pain relief one week after Quadramet administration. Maximal pain relief generally occurs at 3-4 weeks after injection of Quadramet. Patients who experience a reduction in pain may be encouraged to decrease their use of opioid analgesics.

LABORATORY TESTS Because of the potential for bone marrow suppression, beginning 2 weeks after Quadramet administration, blood counts should be monitored weekly for at least 8 weeks, or until recovery of adequate bone marrow function.

In a subset of 31 patients who had serum calcium monitored during the first 21 days after Quadramet infusion, a clear pattern of calcium change was not identified. However, 10 (32%) patients had at least one serum calcium level that was below normal (7.16 to 8.28). The extent to which samarium-153-EDTMP is related to this hypocalcemia is not known. Caution should be exercised when administering Quadramet to patients at risk for developing hypocalcemia.

DRUG INTERACTIONS The potential for additive bone marrow toxicity of Quadramet with chemotherapy or external beam radiation has not been studied. Quadramet should not be given concurrently with chemotherapy or external beam radiation therapy unless the benefit outweighs the risks. Quadramet should not be given after either of these treatments until there has been adequate marrow recovery. (See Warnings Section)

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis in humans given EDTMP in Quadramet, is not likely. Osteosarcomas occurred in a 2-year toxicity and carcinogenicity study of EDTMP administered by gastric intubation to Sprague-Dawley rats, in male rats at 50 mg/kg/day and in male and female rats at 150 mg/kg/day (the dosage was increased to 333 mg/kg/day on day 329 of treatment). Osteosarcomas were not reported in a published chronic dietary study of up to 130 weeks of EDTMP in Fischer 344 rats, at dietary doses up to 100 mg/kg/day (not the maximum tolerated dose). However, at study termination in female Fischer 344 rats this dose was associated with a statistically significant, higher rate of pancreatic islet cell adenomas and carcinomas.

The results of the following genotoxicity assays with non-radioactive samarium-EDTMP were negative: Salmonella reverse mutation (AMES) assay, unscheduled DNA synthesis in rat primary cell culture chromosomal aberration assay in rat lymphocytes, CHO HGPRT forward mutation assay, and mouse bone marrow micronucleus test.

Studies have not been performed to examine the effect of Quadramet on fertility.

PREGNANCY

NURSING MOTHERS

PEDIATRIC USE

ADVERSE EVENTS

TABLE 6: SELECTED ADVERSE EVENTS REPORTED IN ≥ 1.0 % OF PEOPLE WHO RECEIVED QUADRAMET OR PLACEBO IN CONTROLLED CLINICAL TRIALS

ADVERSE EVENT	Placebo N (%)	Quadramet 1.0 mCi/kg N = 199
# Patients with Any Adverse Event	72 (100%)	183 (92%)
Body As A Whole	50 (69%)	100 (50%)
Pain, Flare Reaction	5 (6.9%)	14 (7.0%)
Cardiovascular	19 (26%)	32 (16%)
Arrhythmias	2 (2.8%)	10 (5.0%)
Chest Pain	4 (5.6%)	8 (4.0%)
Hypertension	0	6 (3.0%)
Hypotension	2 (2.8%)	4 (2.0%)
Digestive	44 (61%)	82 (41%)
Abdominal Pain	7 (9.7%)	12 (6.0%)
Diarrhea	3 (4.2%)	12 (6.0%)
Nausea &/or Vomiting	37 (51.4%)	65 (32.7%)
Hematologic & Lymphatic	12 (17%)	54 (27%)
Coagulation Disorder	0	3 (1.5%)
Hemoglobin Decreased	21 (29.2%)	81 (40.7%)
Leukopenia	6 (8.3%)	116 (58.3%)
Lymphadenopathy	0	4 (2.0%)
Thrombocytopenia	8 (11.1%)	136 (68.3%)
Any Bleeding Manifestations*	8 (11.1%)	32 (16.1%)
Ecchymosis	1 (1.4%)	3 (1.5%)
Epistaxis	1 (1.4%)	4 (2.0%)
Hematuria	3 (4.2%)	10 (5%)
Infection	10 (13.9%)	34 (17.1%)
Fever and/or Chills	10 (13.9%)	17 (8.5%)
Infection, Not Specified	4 (5.6%)	14 (7.0%)
Oral Candidiasis	1 (1.4%)	4 (2.0%)
Pneumonia	1 (1.4%)	3 (1.5%)
Musculoskeletal	26 (36%)	55 (27%)
Myasthenia	8 (11.1%)	13 (6.5%)
Pathologic Fracture	2 (2.8%)	5 (2.5%)
Nervous	29 (40%)	59 (30%)
Dizziness	1 (1.4%)	8 (4.0%)
Paresthesia	1 (1.4%)	4 (2.0%)
Spinal Cord Compression	5 (6.9%)	13 (6.5%)
Cerebrovascular Accident/Stroke	0	2 (1.0%)
Respiratory	24 (33%)	35 (18%)
Bronchitis/Cough Increased	2 (2.8%)	8 (4.0%)
Special Senses	11 (15%)	11 (6%)
Skin & Appendages	17 (24%)	35 (18%)
Pruritus	0	2 (1.0%)
Rash	2 (2.8%)	2 (1.0%)

*Includes Gastrointestinal (Gastrointestinal, Rectal) Epistaxis, Hematuria

OVERDOSAGE

DOSAGE AND ADMINISTRATION:

Radiation Dosimetry: The estimated absorbed radiation doses to an average 70 kg adult patient from an intravenous injection of Quadramet are shown in Table 7. The dosimetry estimates were based on clinical biodistribution data using methods developed for radiation dose calculations by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine.

Radiation exposure is based on a urinary voiding interval of 4.8 hours. Radiation dose estimates for bone surfaces assume that radioactivity is deposited on bone surfaces, as noted in autoradiograms of biopsy specimens from 7 patients who received Quadramet. Although electron emissions from ^{153}Sm have energies up to 810 keV, rapid blood clearance of Quadramet and low energy and abundance of gamma emissions generally result in low radiation doses to those parts of the body where the complete decay occurs.

When osteoblastic lesions are present, significantly enhanced localization of the radiopharmaceutical will occur, with correspondingly higher doses to the lesions compared with normal bones and other organs. (See CLINICAL PHARMACOLOGY, Skeletal Uptake and Pharmacodynamics Sections)

TABLE 7

RADIATION ABSORBED DOSES

70 kg ADULT

Target Organ	Rad/mCi	mGy/MBq
Bone Surface	25.0	6.76
Red Marrow	5.70	1.54
Urinary Bladder Wall	3.60	0.097
Kidneys	0.065	0.018
Whole Body	0.040	0.011
Lower Large Intestine	0.037	0.010
Ovaries	0.032	0.0086
Muscle	0.028	0.0076
Small Intestine	0.023	0.0062
Upper Large Intestine	0.020	0.0054
Testes	0.020	0.0054
Liver	0.019	0.0051
Spleen	0.018	0.0049
Stomach	0.015	0.0041

HOW SUPPLIED

STORAGE: