The pH of the solution is 7.0 to 8.5.

The structural formula of samarium lexidronium (anhydrous calc.), 5-46 µg samarium (samarium Sm-153 oxide (152Sm2O3)). It emits both medium-energy beta particles and a gamma calibration.

In clinical studies employing planar imaging techniques, more QUADRAMET® accumulates in osteoblastic metastases than in normal bone with a less than normal bone rate of approximately 5. The mechanism of action of QUADRAMET® is not known.

Skeletal Uptake: The greater the number of metastatic lesions, the more the skeletal uptake of Sm-153 EDTMP. The relationship between skeletal uptake and the size of the metastatic lesions has not been studied. The total skeletal uptake of radioactivity was 65% ± 15% of the injected dose in 453 patients with metastatic lesions from a variety of primary malignancies. In a study of 20 patients with a wide range in the number of metastatic sites, the % of the injected dose (% ID) taken up by bone ranged from 56.3% in a patient with 5 metastatic lesions to 78.7% in a patient with 82 metastatic lesions. If the number of metastatic lesions is fixed, the % of the injected dose is fixed, the % ID taken up by bone for patients who received 0.5 mCi 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, 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, at least 8 months expected survival and had a positive radiographic 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, placebo-controlled clinical trials. These patients had a mean age of 67, and a range 22 to 87 years. Eligible patients who had painful metastatic bone lesions that had failed other treatments, at least 8 months expected survival and had a positive radiographic bone scan. Routine x-rays to evaluate the metastatic lesions were not part of the protocol.

CLINICAL TRIALS
Overall QUADRAMET® was evaluated in 580 patients (see Adverse Events Section for demographic description). Of these patients, 270 (244 men; 26 women) were studied in two non-controlled, blinded, placebo-controlled clinical trials. These patients had a mean age of 67, and a range 22 to 87 years. Eligible patients who had painful metastatic bone lesions that had failed other treatments, at least 8 months expected survival and had a positive radiographic bone scan. Routine x-rays to evaluate the metastatic lesions were not part of the protocol. Of the 270 patients studied, 232 (86%) had prostate cancer and 38 (14%) had other primary tumors. In study A, 80 (68%) of the prostate cancer patients had prostate cancer and 38 (14%) had other primary tumors. In study B, 119 (79%) patients had prostate cancer.

The results of the QUADRAMET® scores in Table 3 are shown in Table 3. In both trials for each of the 4 weeks of study, the more QUADRAMET® scores decreased in patients who received QUADRAMET® (0.5 mCi/kg). In study A, the pain (a) mean Analgesic Use (SD) is in oral morphine equivalents.

Exclusion: For QUADRAMET®, the use of a single- dose glass vials containing 3 mc, with 5550 MBq (150 mCi) of samarium-153 at calibration.

The structural formula is depicted in Samarium lexicronium pentasulfate is.

The ion exchange is expressed as the cumulative activity excreted. The whole body retention is the simple reciprocal of the cumulative urinary activity (see UCLEAR uptake (Section). Blood Clearance of radioactivity from the blood demonstrated biexponential kinetics after intravenous injection in 19 patients (10 men, 9 women) with a variety of primary cancers that were metastatic to bone. The first 30 minutes, the radioactivity (mean ± SD) in the blood decreased to 15% (±) of the injected dose at 1/2 of 5.5 min (± 1.1 min) after 30 min with a half-time clearance from the blood more slowly with a % of 56% of the injected dose remaining in the blood after injection.

Urine: Samarium Sm-153 EDTMP radioactivity 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 less radioactivity was excreted.

Gender Differences: Gender did not affect the samarium Sm-153 EDTMP 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 comparison of values from people in the age range of 22 to 64 compared to the range 65 to 86 years.

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

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

Drug/Drug Interaction
Drug-drug interaction studies have not been studied.

Pharmacodynamics
The beta part of 153Sm-EDTMP travels a maximum distance of 3.0 mm in soft tissue and 1.7 mm in bone. In clinical trials of 78 patients with metastatic bone lesions who had 13 specific bone scan sites evaluated, the presence or absence of 153Sm-EDTMP uptake is similar to the presence or absence of 99mTc diphosphonate uptake (range 67 to 96% agreement depending upon the blood pool and the site of the bone). Whether the amount of 153Sm-EDTMP uptake varies with the size of the lesion or to the presence of osteoblastic component has not been studied. The clinical benefit of Sm-153 EDTMP is patients with osteoblastic lesions is unknown. The relationship of different tumor cell types to clinical response has not been studied.

In the two clinical trials, the patient's multiple myeloma differences. In Study A, the patients did not receive sham injections as an analogic reduction. In Study B, the patients were encouraged to adjust their pain medications as needed. As shown in Table 4, the morphine equivalent analgesic use in Study A generally increased in both the QUADRAMET® and placebo treatment groups, however, the difference between the QUADRAMET® and placebo group change from baseline is not statistically significant. In Study B, the placebo treated patients increased their analgesics by 25% (± 5%), while the QUADRAMET® treated patients decreased their use of oral analgesics.

Therapeutic – For Intravenous Administration
DESCRIPTION: QUADRAMET® is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenebis(oxyethylenemethoxymethylene)phosphonic acid (ESTMP) (QUADRAMET®). It is formulated as a single, sterile, glass, colorless, clear to light amber isotonic solution of samarium Sm-153 EDTMP for intravenous administration. QUADRAMET® does not contain a preservative.

Each milliliter contains 35 mc EDTMP-0.5 mg Ca (as CaEDTA), 141 mg Na (as NaEDTA), equivalent to 44 mg CaEDTA (pH3/2), 5.49 mg ammonium (ammonium chloride), 0.1% (+) activity of approximately 0.1, 0.13 HCl (10 µg µg), and 1,860 and 1,850 MBq (50 5.0 Ci) of samarium-153 at calibration.
INDICATIONS: QUADRAMET® is indicated for the treatment of patients with bone metastases known hypercalcemia to EDTMP or sim- ilar indications.

WARNINGS: QUADRAMET® causes severe marrow suppression. In clinical trials, white blood cell (WBC) counts decreased to a rate of approximately 40% per week in 58% of patients within 3 to 5 weeks after QUAD- RAMET® administration, and neutrophil counts to a rate of 40% per week in 6 weeks after treatment. In 32% of patients, the nadir occurred by 8 weeks. The grade of marrow toxicity is shown in Table 6.

Although not demonstrated, it is probable that cumulative effects of QUADRAMET® over an extended period of time may result in irreversible bone marrow suppression. Because of this potential, patients should be counseled to take a single administration of a dose of QUADRAMET® until there has been time for a recovery of adequate bone marrow function. This recovery can be anticipated to occur in 4 to 6 months in most patients, but may occur later in extremely debilitated patients.

Because concomitant hydration is recom- mendable to prevent dehydration during administration of QUADRAMET®, appropriate monitoring and care during and after administration of the drug should be used in patients with a history of renal impairment, cardiac failure or renal insufficiency.

This drug should be used with caution in patients with a history of bone marrow depression. See Warnings.

Special precautions: Dose-Fractionation: Frequency of administration may be treated to minimize radiation exposure of clinical personnel and other patients in the environment.

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Special precautions: In patients with cancer, the potential for addiction to these agents is real and must be considered in the management of these patients. As with any other potent drug, patients should be followed after administration of QUADRAMET®.

PRECAUTIONS: As with other radiophar- macological drugs, QUADRAMET® can cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies have not been conducted in animals or pregnant women. Women of childbearing age should not have a pregnancy test before administra- tion of QUADRAMET®. If this drug is used during pregnancy, or if a patient becomes pregnant while taking this drug, the patient should be apprised of the potential risks to the fetus. Women of childbearing age should not breastfeed before administration of QUADRAMET®. If a patient is known or suspected to be pregnant, patients should be advised to use an effective contraceptive method. See Warnings.

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