upake and skeletal uptake of Sm-153 radioactivity. The relationship between skeletal uptake and the size of the metastatic lesions has not been studied. The total skeletal uptake of radioactivity was 65.3% ± 1.5% of the injected dose in 435 patients with metastatic lesions from a variety of primary malignancies. In a study of 22 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 76.7% in a patient with 49 metastatic lesions. The % ID is fixed, over the range 0.1 to 3.0 mCi/kg, the % ID taken up by bone is the same regardless of the dose.

**Metabolism:** The complex formed by samarium and EDTMP is excreted as an intact complex and as a mixture of Sm and EDTMP when excreted. If the patient’s urine contains enough EDTMP, the Sm will be excreted as radioactive EDTMP when excreted. As shown by an analysis of urine samples from patients (n=5) administered samarium Sm-153 EDTMP. Metabolic products of samarium Sm-153 EDTMP were not detected in humans.

**Elimination:** For QUADRAMET®, calculations of the % ID detected in the whole body after intravenous injection of Sm-153 EDTMP were corrected for radionuclide decay. The clearance of activity through the urine is expressed as the cumulated activity excreted. The whole body retention is the simple reciprocal of the cumulated urine activity. (See Table 1 above).

Blood: Clearance of radioactivity from the blood demonstrated bieponential kinetics after intravenous injection in 19 patients (10 men, 9 women) with a variety of primary cancers that were metastatic to bone. Over the first 30 minutes, the radioactivity (mean ± SD) in the blood decreased 0.95% ± 0.68% of the injected dose with a t½ of 1/2 of 0.5 ± 1.1 minutes. After 30 minutes, the radioactivity cleared from the blood more slowly with a t½ of 65.4 ± 9.6 minutes. Less than 1% of the dose was retained in the blood for 5 hours 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 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. Whether the amount of bone uptake varies with the size of the bone lesion is fixed, over the range 0.1 to 3.0 mCi/kg, the % ID taken up by bone is the same regardless of the dose.

**Dosage for each of the 4 weeks of study, the mean AUPC scores decreased in placebo and treatment group.

**Placebo**

**AUPC**

**Drug**

**Drug-Drug Interaction**

Drug-drug interaction studies have not been studied.

**Pharmacodynamics**

The beta particle of Sm-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 scans evaluated, the presence or absence of Sm-EDTMP uptake varies with the size of the bone lesion or to the presence of osteolytic com-pontents 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 QUADRAMET® was evaluated in 580 patients (see Adverse Events Section for additional information). Of these, 270 (244 men, 26 women) were studied in two randomized, blinded, placebo controlled clinical trials. These patients had a mean age of 67 years, and a range 22 to 87 years. Eligible patients had painful metastatic bone lesions from solid tumors, and had at least 6 month expected survival and had a positive radionuclide bone scan. Routine rXAs 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 visual analogue scale rated from 0 (no or low pain) to 10 (excruciating pain). The area under the pain curve (AUPC) was obtained by integrated the daily pain scores with bi-weekly recorded doses in comparison to baseline in a group of 100 (48%) 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 osteolytic 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® causes bone marrow suppression. In clinical trials, while bone counts and platelet counts decreased to a nadir of approximately 40% to 50% of baseline in 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.

**Before QUADRAMET® is administered, consideration should be given to the pa-tient's current clinical and hematologic status and bone marrow response history to chemotherapy and other therapeutic agents.**

**Drug safety and benefit studies** have not been conducted in animals or pregnant women. Women of childbearing age should have a negative pregnancy test before administration of QUADRAMET®.

**If this drug is used during pregnancy, or if a patient becomes pregnant after taking this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing age should have a negative pregnancy test before administration of QUADRAMET®.**

Use of this patient should be used as an effective method of contraception after the administration of QUADRAMET®.

**The vial stopper contains dry natural rubber latex and may cause allergic reac-tions in individuals sensitive to latex.**

**PRECAUTIONS:** EDTMP is a chelating agent. Although the chelating effects have not been evaluated thoroughly in humans, dogs that received non-radioactive samarium EDTMP (6 times the human dose based on body weight, 3 times based on surface area) had changes of EDG (changes in the presence of the hypecalcemia). The causual relationship between the hypocalcemia and EG changes has not been studied. Whether QUADRAMET® causes electro-cardiographic changes or arrhythmias in humans has not been studied. Careful and appropriate monitoring should be given when administering QUADRAMET® to patients (See Laboratory Tests).

Because concomitant hydration is recommended to promote the urinary excretion of QUADRAMET®, appropriate monitoring and consideration of additional supportive treatment should be provided in patients with a history of congestive heart failure or renal insufficiency.
This drug should be used with caution in patients with compromised bone marrow reserves. See Warnings.

Skeletal: Spinal cord compression frequently occurs in patients with known metastases to the cervical, thoracic, or lumbar spine. In clinical studies of QUADRAMET®, spinal cord compression was reported in 10% of patients who received placebo and in 8.3% of patients who received 1.0 mCi/kg QUADRAMET®. QUADRAMET® is not indicated for treatment of spinal cord compression. QUADRAMET® administration for pain relief of metastatic bone disease does not prevent development of spinal cord compression. When there is a clinical suspicion of spinal cord compression, appropriate diagnostic and therapeutic measures must be taken immediately to avoid permanent disability.

Radiotherapeutic agents should be used only by physicians who are qualified by training and experience in the safe use and handling of radioisotopes and whose experience and training have been approved by the appropriate government agency authorized to license the use of radioisotopes.

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 the patient in the environment.

Special precautions, such as bladder cateterization, should be taken with incontinent patients to minimize the risk of radioactive contamination of clothing, bed linens, 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 the excreted urine. To help protect themselves and others in their environment, precautions should be taken to be followed for 12 hours after 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 patients should wash their hands thoroughly. If blood or urine gets onto clothing, the clothing should be washed separately, or stored for 1-2 weeks to allow for decay of the radioisotope.

In some patients there has 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 injection. 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 injection of QUADRAMET®, blood counts should be monitored weekly for at least 6 weeks, or until recovery of adequate bone marrow function.

In a subset of 21 patients who had serum calcium monitored during the first 2 hours after QUADRAMET® infusion, a clear pattern of calcium change was not identified. However, 10 of 21 patients showed a peak in serum calcium that was about below normal (7.16 to 8.28). The extent to which sarum153-EDTMP is related to this hypercalcemia is not known. Caution should be exercised when administering QUADRAMET® to patients at risk for developing hypercalcemia.

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 time for adequate marrow recovery. (See Warnings Section).

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY Carcinogenesis in humans given EDTMP in a 2-year toxicity/carcinogenicity study of EDTMP administered by gastric intubation to Fisher 344 rats, this dose was associated with statistically significantly higher rate of osteosarcomas. Osteosarcomas were not reported in a published chronic dietary study in rats, where EDTMP was negative: Sal monella reverse mutation (AMES) assay, unscheduled DNA synthesis in rat liver 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 assess the effect of QUADRAMET on fertility.

PREGNANCY Pregnancy Category D. See Warnings Section.

NURSING MOTHERS It is not known whether QUADRAMET® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from QUADRAMET®, a decision should be made whether to continue nursing or to administer the drug. If QUADRAMET® is administered, formula feedings should be substituted for breast feedings.

PEDIATRIC USE Safety and effectiveness in pediatric patients before the age of 16 years have not been established.

ADVERSE EVENTS

Adverse events were evaluated in a total of 580 patients who received QUADRAMET® in clinical trials. Of the 580 patients, there were 472 men and 108 women with a mean age of 66 (range 20 to 87).

In an additional 200 patients who received QUADRAMET® in uncontrolled clinical trials, adverse events that were reported at a rate of ≥ 0.5% in ≥ 5 patients for QUADRAMET® 1.0 mCi/kg in any clinical trial include: alopecia, angina, congestive heart failure, sinus bradycardia, and vasodilations.

OVERDOSE: Overdose with QUADRAMET® has not been reported. An anti- toxin for QUADRAMET® overdose is not known. The anticipated complications of overdose would likely be secondary to bone marrow suppression from the radioactivity of ≥1Sm, or secondary to hypocalcemia and cardiac arrhythmias related to the EDTMP.

DOSEAGE AND ADMINISTRATION: The recommended dose of QUADRAMET® is 1.0 mCi/kg administered intravenously over a period of one minute through a se- curely placed catheter followed with a saline flush. Dose adjustment in pa- tients at the extremes of weight have not been studied. Caution should be exercised when determining the dose in very thin or very obese patients.

The dose should be measured by a suitable radioactivity calibration system, such as a radioscope dose calibrator, immediately before administration.

The dose of radioactivity to be administered and the patient should be verified before administering QUADRAMET®. Patients should not be released until their radioactivity levels and exposure rates comply with federal and local regulations.

The patient should ingest (or receive by i.v. administration) a minimum of 500 mL (2 cups) of fluids prior to injection and should void as soon as possible after injection to minimize radiation exposure to the body.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit. The solution should not be used if it is cloudy or if it contains particulate matter.

QUADRAMET® contains calcium and may be incompatible with solutions that con- tain molecular oxygen that can complex with and form calcium precipitates.

QUADRAMET® should not be diluted or mixed with other solutions.

Thaw at room temperature before administration and use within 8 hours of thawing.

Radiation Dosimetry: The estimated absorbed radiation doses to an average 70 kg adult patient from an i.v. injection of QUADRAMET® are shown in Table 7. The dosimetry estimates were based on clinical biodistribution studies using methods developed for radiation dose calculations by the Medical Internal Radiation Dose (MIRD) 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 and marrow assume that radioactivity is deposited on bone surfaces, as noted in autoradiograms of biopsy bone samples in 7 patients who re- ceived QUADRAMET®. Although electron emissions from 153Sm are abundant, with energies up to 810 keV, rapid blood clearance of QUADRAMET® and low energy emission makes significant absorbed photon emissions generally result in low radioactivity doses to those parts of the body where the complex does not localize.

When blastic osteosclerosis 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, Skele- tual uptake and Pharmacodynamics Sections).

**TABLE 7**

<table>
<thead>
<tr>
<th>Radiation Absorbed Doses</th>
<th>70 kg Adult</th>
<th>Activity</th>
<th>mCi/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone Surfaces</td>
<td>25.0</td>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>Red Marrow</td>
<td>5.70</td>
<td>1.54</td>
<td></td>
</tr>
<tr>
<td>Urinary Bladder Wall</td>
<td>3.60</td>
<td>0.97</td>
<td></td>
</tr>
<tr>
<td>Kidneys</td>
<td>0.865</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Whole Body</td>
<td>0.40</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Lower Large intestine</td>
<td>0.027</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>0.002</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Muscle</td>
<td>0.028</td>
<td>0.0076</td>
<td></td>
</tr>
<tr>
<td>Small Intestine</td>
<td>0.013</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Upper Large Intestine</td>
<td>0.020</td>
<td>0.0054</td>
<td></td>
</tr>
<tr>
<td>Tests</td>
<td>0.020</td>
<td>0.0054</td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>0.019</td>
<td>0.0031</td>
<td></td>
</tr>
<tr>
<td>Spleen</td>
<td>0.018</td>
<td>0.0041</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.015</td>
<td>0.0041</td>
<td></td>
</tr>
</tbody>
</table>

HOW SUPPLIED QUADRAMET® is supplied frozen in a single-dose 10 ml glass vial containing 1850 ± 185 mCi/mL (50 ± 5 mCi) of samarium-153, at calibration. QUADRAMET® is available in the following size: NDC #1 1994-016-01 3.0 mCi, full size with total activity of 5550 M Ci (150mCi). The vial is shipped in a lead shield; a package insert is included. The drug product expires 56 hours after the time of calibration noted on the label, or 8 hours after thawing, whichever is earlier.

Storage: Store frozen at −10°C to −20°C (4°F to −6°F) in a lead shield container. Storage and disposal of QUADRAMET® should be controlled in a manner that complies with the appropriate regulations of the government agency authorized to license the use of this radionuclide.

This radioactive drug is approved for distribution to persons licensed pursuant to the Code of Massachusetts Regulations 105 CMR 120.100 for the lists used in 105 CMR 120.589 or under equivalent regulations of the U.S. Nuclear Regulatory Commission, an Agreement State or a Licensing State.

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