

PRODUCT
INFORMATION

QUADRAMET[®]

Samarium (¹⁵³Sm) Lexidronam Pentasodium Injection

Description

Quadramet is supplied in single dose vials, containing 6 GBq of radioactive Samarium-153 complexed with ethylenediaminetetra methylenephosphonic acid monohydrate (EDTMP) in 3 ml, as a frozen, sterile, colourless to light amber, preservative free, isotonic solution for intravenous injection. It contains no antimicrobial agent.

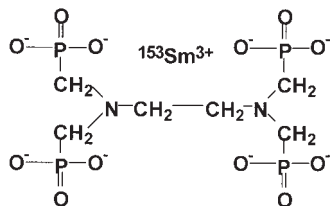
Each ml of solution contains:

- less than 200 µg of total Samarium
- 35 mg EDTMP (calculated as the monohydrate)
- 2.9 mg calcium ion
- 8.1 mg sodium ion and chloride ion as a result of the manufacturing process.

The radioactive concentration is between 1.8 - 2.2 GBq/ml at calibration. The pH of the solution is 7.0 to 8.5

Due to the neutron flux limitations at the Australian Nuclear reactor Quadramet manufactured in Australia has a lower specific activity of total Samarium (<200µg/ml) compared with 20-46µg/ml for the USA and European products.

The structural formula is:



Physical Characteristics of ¹⁵³Sm

Samarium -153 is produced in high yield and purity by neutron irradiation of isotopically enriched samarium-152 oxide. It emits both medium energy beta particles and an imageable gamma photon, and has a physical half-life of 46.7 hours. Samarium -153 has average and maximum beta particle ranges in water of 0.5 mm and 3.0 mm, respectively. The primary radiation emissions of Samarium 153 are shown in Table 1.

Table 1: Principal Radiation Emission data

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

Maximum energies are listed for the beta particles ie E_{max}. The average beta particle energy is 233 keV.

Table 2. Physical Decay Chart

Time(hr)*	Factor	Time(hr)*	Factor
-48.0	2.05	+1.0	0.99
-36.0	1.71	+2.0	0.97
-24.0	1.43	+3.0	0.96
-20.0	1.35	+4.0	0.94
-16.0	1.27	+6.0	0.91
-12.0	1.20	+8.0	0.89
-8.0	1.13	+12.0	0.84
-6.0	1.09	+16.0	0.80
-4.0	1.06	+20.0	0.74
-3.0	1.05	+24.0	0.70
-2.0	1.03	+36.0	0.58
-1.0	1.02	+48.0	0.49

* Time = hours before(-) or after(+) calibration.

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External Radiation

The specific gamma-ray constant for Samarium 153 is 2.44×10^{-5} mGy/MBq/hr at 1 metre. The half-value thickness of lead (Pb) for Samarium Sm-153 is approximately 0.10 mm. The use of 1 mm of lead will decrease the external radiation exposure by a factor of approximately 1,000. Quadramet should be stored frozen in a shielded container until use.

Pharmacology

Quadramet has an affinity for skeletal tissue and concentrates in areas of bone turnover in intimate association with hydroxyapatite. Studies in rats have demonstrated that Quadramet is cleared rapidly from the blood and localises to growing areas of bone matrix, specifically the layer of osteoid undergoing mineralisation. In clinical studies employing planar imaging techniques, Quadramet accumulates with a lesion-to-normal bone ratio of approximately 5 and a lesion-to-soft tissue ratio of approximately 6. Lesion-to-normal bone ratios in animals were approximately 17. Thus, areas of metastatic involvement can accumulate significantly greater amounts of Quadramet than surrounding normal bone.

Pharmacokinetics

In patients, Quadramet is rapidly cleared from the blood. Thirty minutes after injection of 37 MBq/kg of the agent to 12 patients, only $10.9 \pm 6\%$ (mean \pm SD) of the administered dose remained in plasma. At 6 hours, plasma radioactivity had decreased to $0.5 \pm 0.3\%$ of the administered dose. Urinary excretion occurred predominantly during the first 6 hours ($38.9 \pm 24.4\%$). Analysis of urine samples from patients administered Quadramet in

North America found the radioactivity to be present as the intact complex. Less urinary excretion occurred in patients who had extensive bony metastases, regardless of the amount of radiopharmaceutical administered.

Total skeletal uptake of Quadramet in international studies of 453 patients with a variety of primary malignancies was $65.5 \pm 15.5\%$ of the administered dose.

A positive correlation was found between skeletal uptake and the number of metastatic sites. In contrast, skeletal uptake was inversely proportional to plasma radioactivity at 30 minutes and was unaffected by the amount of Quadramet administered.

Indications and Usage

Quadramet is indicated for the relief of bone pain in patients with painful osteoblastic skeletal metastases as indicated by positive bone scan. The presence of bone metastases should be confirmed prior to therapy.

Contraindications

Since Quadramet causes myelosuppression, its use is contraindicated in patients who have severely compromised bone marrow reserves (see also PRECAUTIONS)

Quadramet should not be given concurrently with chemotherapy or external beam radiation therapy, because of potential for additive effects on bone marrow.

Quadramet may be given subsequent to either of the treatments after allowing for adequate marrow recovery.

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

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Precautions

General

Radiopharmaceuticals should be used only by physicians who are qualified by specific training in the safe use and handling of radionuclides produced by nuclear reactor or particle accelerator and whose experience and training have been approved by the appropriate government agency authorised to licence the use of radionuclides.

To minimise radiation exposure to clinical personnel and other patients, the patient should be treated in a facility with appropriate shielding.

Due care and appropriate safety measures should always be practiced.

Use with caution in the following circumstances

Use of Quadramet in patients with evidence of compromised bone marrow reserve from previous therapy or disease involvement is not recommended unless the potential benefit of the treatment outweighs its risks. Decreases in white blood cell (WBC) counts and platelet counts were observed in patients receiving Quadramet in clinical trials. Counts decreased to a nadir of approximately 40% to 50% of baseline in a predictable fashion 3 to 5 weeks after a dose, and generally returned to pretreatment levels by 8 weeks post treatment. These changes were rarely clinically significant. A few patients who experienced Grade 3 or 4 haematopoietic toxicity usually either had a history of recent external beam radiation therapy or chemotherapy or had rapidly progressive disease with probable bone marrow involvement. In general, repeat administration of Quadramet should be based on an

individual patient's response to prior treatment, current symptoms and haematologic status. The treatment should not be repeated for at least 8 weeks after a previous dose and only then when WBC and platelet counts have sufficiently recovered.

Since Quadramet is myelosuppressive, it should be administered with caution in patients who may be candidates for other myelosuppressive therapies, including those patients with extensive soft tissue metastases.

Conditions that require urgent surgical treatment, such as impending pathological fracture and impending spinal cord compression, should be excluded before Quadramet is administered.

Renal impairment. The use of Quadramet in patients with renal impairment has not been studied.

Check the following before use

Verification of the dose to be administered and patient identification is necessary prior to administration of Quadramet.

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

The product is supplied frozen, do not use if the solution is not frozen or thawed on receipt.

Quadramet contains calcium and may be incompatible with solutions that contain molecules that complex with and form calcium precipitates and therefore should not be diluted or mixed with other solutions.

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Carcinogenesis, Mutagenesis, Impairment of Fertility

EDTMP alone, caused metaphyseal osteosclerosis and osteosarcomas at oral doses of 50 mg/kg/day and greater in a 2-year study in rats. Non-radioactive Samarium -EDTMP was not genotoxic in a battery of assays for gene mutations, chromosomal and DNA damage, but, in all the tests except the Salmonella typhimurium reverse- mutation assay, the concentrations/doses of drug employed were insufficient to cause toxicity and the results may have been invalid.

No studies have been done to assess the effect of Quadramet on fertility.

Use in Pregnancy (Category D.)

Quadramet may cause harm to the foetus if administered during pregnancy. There are no adequate and well controlled studies in pregnant women or animals. If this drug is used during pregnancy, or the patient becomes pregnant after taking this drug, the patient should be apprised of the potential hazard to the foetus.

Women of child-bearing potential should be advised to avoid becoming pregnant.

Use in Lactation

It is not known whether Quadramet is excreted in human milk. As the drug has a serious potential to harm breast-fed infants, Quadramet should not be used by lactating patients.

Paediatric Use

Safety and effectiveness in children below the age of 18 years have not been established.

Interactions with other Drugs

Quadramet should not be given concurrently with chemotherapy or external beam radiation therapy, because of potential additive effects on bone marrow.

Quadramet may be given subsequent to either of these treatments after allowing for adequate marrow recovery.

Adverse Reactions

The toxicities of Quadramet result from predictable myelosuppression. In clinical trials, WBC and platelet nadirs were usually observed 3 to 5 weeks after treatment with values generally returning toward normal by week 8.

Thrombocytopenia and leucopenia were generally mild to moderate in nature. More profound marrow toxicity should be managed by conventional means.

One patient with rapidly progressive prostate cancer and evidence of disseminated intravascular coagulation developed thrombocytopenia and experienced a fatal cerebrovascular accident 4 weeks after receiving Quadramet.

Flare reactions, ie., worsening of pain shortly after treatment, occurred in a small number of patients who received Quadramet. The flare reactions generally occurred within 3 days after treatment and were usually mild, transient, self limiting and controllable with analgesics.

The most common adverse events observed in controlled clinical studies of Quadramet, are given in Table 3. (Reference: US PI for Quadramet Feb 1997. - 513145-0297)

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TABLE 3

Selected Adverse Events Reported in > 1.0% Of People Who Received Quadramet Or Placebo In Controlled Trials

ADVERSE EVENT	PLACEBO N = 90	Quadramet 1.0 mCi/kg N = 199
Patients with Any Adverse Event	72 (80%)	169 (85%)
Body As A Whole	56 (62%)	100 (50%)
Pain Flare reaction	5 (5.6%)	14 (7.0%)
Cardiovascular	19 (21%)	32 (16%)
Arrhythmias	2 (2.2%)	10 (5.0%)
Chest Pain	4 (4.4%)	8 (4.0%)
Hypertension	0	6 (3.0%)
Hypotension	2 (2.2%)	4 (2.0%)
Digestive	44 (49%)	82 (41%)
Abdominal Pain	7 (7.8%)	12 (6.0%)
Diarrhoea	3 (3.3%)	12 (6.0%)
Nausea & /or Vomiting	37 (41.1%)	65 (32.7%)
Haematologic & Lymphatic	12 (13%)	54 (27%)
Coagulation Disorder	0	3 (1.5%)
Haemoglobin Decreased	21 (23.3%)	81(40.7%)
Leukopenia	6 (6.7%)	118(59.3%)
Lymphadenopathy	0	4 (2.0%)
Thrombocytopenia	8 (8.9%)	138(69.3%)
Any Bleeding manifestations *	8 (8.9%)	32 (16.1%)
Ecchymosis	1 (1.1%)	3 (3.0%)
Epistaxis	1 (1.1%)	4 (2.0%)
Hematuria	3 (3.3%)	10 (5%)
Infection	10 (11.1%)	34 (17.1%)
Fever and/or Chills	10 (11.1%)	17 (8.5%)
Infection, not specified	4 (4.4%)	14 (7.0%)
Oral Moniliasis	1 (1.1%)	4 (2%)
Pneumonia	1 (1.1%)	3 (1.5%)
Musculoskeletal	28 (31%)	55 (27%)
Myasthenia	8 (8.9%)	13 (6.5%)
Pathologic Fracture	2 (2.2%)	5 (2.5%)
Nervous	39 (43%)	59 (30%)
Dizziness	1 (1.1%)	8 (4.0%)
Paresthesia	7 (7.8%)	4 (2%)
Spinal Cord Compression	5 (5.5%)	13 (6.5%)
Cerebrovascular Accident/stroke	0	2 (1.0%)
Respiratory	24 (27%)	35 (18%)
Bronchitis/Cough Increased	2 (2.2%)	8 (4.0%)
Special Senses	11 (12%)	11 (6%)
Skin & Appendages	17 (19%)	13 (7%)
Purpura	0	2 (1%)
Rash	2 (2.2%)	2 (1%)

*includes haemorrhage (gastrointestinal, ocular) reported in <1%.

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Any suspected adverse reaction should be reported to

Office of Medicine Safety Monitoring
Therapeutic Goods Administration
PO Box 100, Woden ACT 2606
Fax: 02 6232 8180

Dosage and administration

- The recommended dose of Quadramet is 37 MBq/kg administered intravenously as a bolus through an established i.v. line over a period of one minute.
- The patient dose should be measured by a suitable radioactivity calibration system, such as a radioisotope dose calibrator, immediately before administration.
- To calibrate dose calibrators for Quadramet, an accurately measured secondary standard of Samarium -153 can be obtained from the manufacturer.
- The pH of the drug product should be between 7 and 8.5.
- The patient should be encouraged to ingest (or receive by i.v. administration) a minimum of 500 ml (2 cups) of fluids prior to injection and should be encouraged to void as often as possible after injection to minimise radiation exposure to the bladder.
- No data is available on the use of Quadramet in patients with renal impairment.
- For incontinent patients, special precautions such as bladder catheterisation, should be

taken following administration to minimise the risk of radioactive contamination of clothing, bed linen and the patient's environment.

- Urinary excretion of Quadramet is essentially complete by 6 hours.
- The solution does not contain any anti microbial, discard any residue.
- Currently, there are no Australian regulations or guidelines about discharge of patients given Quadramet. Regulations in the United States state that a patient receiving Quadramet may be discharged providing the external exposure is <0.05 mSv/hr at a distance of 1 metre. Measurements taken during US clinical trials indicated that such a level is only attained after administration of very large amounts of Sm-153 (~8 GBq). In general these limits are not exceeded even immediately after administration.
- Blood counts should be monitored weekly, beginning 2 weeks after administration of Quadramet for at least 8 weeks, or until recovery of adequate bone marrow function.

Overdosage

The absolute maximum amount of Quadramet that can be safely administered has not been determined. In early clinical trials, single doses as high as 111 MBq/kg were administered; the highest absolute dose received was 11 GBq. The maximum tolerated dose was 93 MBq/kg in patients with prostate cancer and 56 MBq/kg in patients with breast cancer who were heavily pretreated with chemotherapy. There is no known antidote for Quadramet overdose.

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The anticipated complications of overdose would be secondary to bone marrow suppression.

Radiation Dosimetry

The estimated absorbed radiation doses to an average adult patient from an i.v. injection of Quadramet are shown in Table 4. 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.

Because Quadramet is excreted in the urine, radiation exposure was 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, in accordance with autoradiograms of bone samples taken from patients who received Quadramet. Although electron emissions from Samarium-153 are abundant, with energies up to 810 keV, rapid blood clearance of Quadramet and low energy and abundant photon emissions generally result in low radiation doses to those parts of the body where the complex does not localise.

When blastic osseous metastases are present, significantly enhanced localisation of the radiopharmaceutical will occur, with correspondingly higher doses to the metastases compared with normal bone and other organs.

The maximum additional effective dose which may result from the administration of 37

MBq/kg to a 70 kg patient from the presence of impurity ¹⁵⁴Eu at the maximum permitted level is 0.5 mSv/year.

Table 4: Radiation Absorbed Doses

Target organ	mGy/MBq	mGy/37MBq
Bone surfaces	6.76	251
Red marrow	1.54	57
Urinary bladder wall	0.97	36
Kidneys	0.018	0.67
Lower large intestine	0.010	0.37
Ovaries	0.0086	0.32
Muscle	0.0076	0.28
Small Intestine	0.0062	0.23
Upper large intestine	0.0054	0.20
Testes	0.0054	0.20
Liver	0.0051	0.19
Spleen	0.0049	0.18
Stomach	0.0041	0.15
Whole Body	0.011	0.41

Effective dose: 11.43 mSv /37 MBq
Reference: ICRP 60 (1991) 1990
Recommendations of the International
Commission on Radiological Protection.

Presentation

The product is supplied as a frozen sterile aqueous solution of Samarium [¹⁵³Sm] Lexidronam pentasodium in a 10 ml vial.

The vial is contained in a 6 mm lead pot.

The product should be thawed and administered at 37 MBq/kg within 8 hours after thawing.

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Expiry

Quadramet expires after 48 hours of the calibration time and date given on the label, or 8 hours after thawing, whichever is earlier.

Storage

Store frozen at -10 to -20 degrees Celsius in a shielded container.

Storage and disposal of all radioactive wastes should be carried out in accordance with the NH & MRC "Code of Practice for the disposal of Radioactive wastes by the user." 1985.

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Contact Details

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ANSTO Health is a commercial enterprise of the Australian Nuclear Science and Technology Organisation (ANSTO), which is located at Lucas Heights, in Sydney, N.S.W.

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