MAYO CLINIC

200 First Street SW
Rochester, Minnesota 55905
507-284-2511

September 19, 2007

NIOSH Mailstop: C-34
Robert A. Taft Lab.
4676 Columbia Parkway
Cincinnati, OH 45226

Re: Process for updating the list of hazardous drugs (Appendix A) for the NIOSH Alert on Hazardous Drugs
NIOSH Docket #105

Dear Madams/Sirs:

Thank you very much for allowing me an opportunity to comment on the new drugs which were added to the existing list of hazardous drugs. These 62 drugs were recently evaluated by the National Institute for Occupational Safety and Health (NIOSH), and were considered by NIOSH to have one or more characteristic of a hazardous drug as defined by NIOSH.

NIOSH's intention of identifying drugs that may be hazardous to health care workers who handle the above drugs is a valuable one. However, I do not think that the two radiopharmaceuticals as listed below should be placed in the NIOSH "hazardous drugs" category, and I would like to provide you with the rationale for the above suggestion.

1. Metastron™ (Strontium-89 Chloride Injection)
2. Quadramet® (Samarium Sm 153 Lexidronam Injection)

Please note that my comments/suggestions as follows do not necessarily represent the viewpoints of the Mayo Clinic, the Society of Nuclear Medicine (Chair, Committee on Pharmacopeia), or the United States Pharmacopeia (Acting Chair, Expert Committee on Radiopharmaceuticals and Medical Imaging Agent; member, Ad Hoc Advisory Panels – Pharmaceutical Compounding – Sterile Preparations <797>).

Metastron™ (Strontium-89 Chloride Injection)

According to the preliminary list of the "New FDA Drugs and Warning Fitting NIOSH Criteria for Hazardous Drugs 2006", the column titled "NIOSH Hazardous Drug Criteria" has the following information identified to the above drug:

1. Cancer (carcinogenicity): +
2. Preg Cat (teratogenicity or other developmental toxicity): D
3. Repro Tox (reproductive toxicity): NT
4. Organ Tox (organ toxicity at low doses): (blank)
5. Geno Tox (genotoxicity): NT

+ = characteristic of drug fits NIOSH definition.
NT = Not Tested.
Pregnancy Category D - There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Cancer (carcinogenicity)

As per the package insert of Metastron™ (Strontium-89 Chloride Injection) – see Attachment 1, 75% (33 out of 40) of the tested rats injected with the above agent in 10 consecutive monthly doses of either 250 or 350 μCi/kg showed malignant bone tumors developed after a latency period of approximately 9 months. It seems that human carcinogenicity profile has not been established for Metastron™ (Strontium-89 Chloride Injection) as the package insert (Attachment 1) does not have any information about the human toxicity evaluation on the above drug product.

With regard to the above animal study, the administered dose of Metastron™ (Strontium-89 Chloride Injection) is 4-9 times of the recommended dose for human subjects (i.e., 40-60 μCi/kg). In addition, repeated administrations of Metastron™ (Strontium-89 Chloride Injection) is not recommended for patients at intervals of less than 90 days, whereas the rats of the above-mentioned test were subjected a repeated dose for 10 consecutive months.

Therefore, it does not seem to be appropriate to extrapolate the above animal data to human situation; and it is inadequate to use the package insert (Attachment 1) as a source to support the classification of Metastron™ (Strontium-89 Chloride Injection) as a carcinogen to human subjects.

Preg Cat (teratogenicity or other developmental toxicity)

Even though "Pregnancy Category D" is listed in the section titled "Pregnancy" of Metastron™ (Strontium-89 Chloride Injection) package insert (Attachment 1). The information (see excerpt below) as listed in the "Warnings" section of the package insert (Attachment 1) seems to be inconsistent with the above classification (i.e., "Pregnancy Category D").

Metastron may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women.

The NIOSH designation of "Pregnancy Category D" stipulates that there is positive evidence to link human fetal risk to the drug of interest. Since there is no clear evidence of risk to human fetus in regard to Metastron™ (Strontium-89 Chloride Injection), it is inaccurate to assign the "Pregnancy Category D" to the above drug. It seems to me that the description of NIOSH's "Pregnancy Category C" (see below) may be a more suitable pregnancy category to be designated to Metastron™ (Strontium-89 Chloride Injection).

Pregnancy Category C

Either studies in animals have revealed adverse effects on the fetus (teratogenic or embryocidal or other) and there are no controlled studies in women, or studies in women and animals are not available. Drugs should be given only if the potential benefit justifies the potential risk to the fetus.

As such, the NIOSH Hazardous Drugs Criteria listing for Metastron™ (Strontium-89 Chloride Injection) should be revised as follows:

1. Cancer (carcinogenicity): +/- or (blank)
2. Preg Cat (teratogenicity or other developmental toxicity): C
3. Repro Tox (reproductive toxicity): NT
4. Organ Tox (organ toxicity at low doses): (blank)
5. Geno Tox (genotoxicity): NT

+/- = mixed characteristics

Based on the above revised evaluation outcome, Metastron™ (Strontium-89 Chloride Injection) should be placed in the list of the "New FDA Drugs and Warning Not Fitting NIOSH Criteria for Hazardous Drugs 2006" similar to various other drugs with comparable NIOSH assessment outcomes that are placed in the above "Not Fitting" list.

Quadramet® (Samarium Sm 153 Lexidronam Injection)

As per the preliminary list of the "New FDA Drugs and Warning Fitting NIOSH Criteria for Hazardous Drugs 2006", the column titled "NIOSH Hazardous Drug Criteria" has the following "rating" assigned to the above drug:

1. Cancer (carcinogenicity): +
2. Preg Cat (teratogenicity or other developmental toxicity): D
3. Repro Tox (reproductive toxicity): NT
4. Organ Tox (organ toxicity at low doses): (blank)
5. Geno Tox (genotoxicity): --

+ = characteristic of drug fits NIOSH definition.
-- = characteristic of drug does not fit NIOSH definition.
NT = Not Tested.
Pregnancy Category D - There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).

Cancer (carcinogenicity)

Please refer to the following quotation taken from the package insert of Quadramet® (Samarium Sm 153 Lexidronam Injection) – see Attachment 2:

Carcinogenesis in humans given EDTMP, in QUADRAMET®, is not likely. Osteosarcomas occurred in a 2-year toxicity/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 Fisher 344 rats, at dietary doses up to 100 mg/kg/day (not the maximum tolerated dose). However, at study termination in female Fisher 344 rats, this dose was associated with statistically significantly higher rate of pancreatic islet-cell adenomas and carcinomas.

Hence, the "Cancer (carcinogenicity)" criteria for Quadramet® (Samarium Sm 153 Lexidronam Injection) should be marked as "- -" (i.e., characteristic of drug does not fit NIOSH definition.)

Preg Cat (teratogenicity or other developmental toxicity)

Although "Pregnancy Category D" is listed in the section titled "Pregnancy" of Quadramet® (Samarium Sm 153 Lexidronam Injection) package insert (Attachment 2). The information (see excerpt below) as listed in the "Warnings" section of the package insert seems to be contradictory to the above classification (i.e., "Pregnancy Category D").

Adequate and well controlled studies have not been conducted in animals or pregnant women. Women of childbearing age should have a negative pregnancy test before administration of QUADRAMET®.

Since neither animal nor human study has not been carried out, the NIOSH designation of "Pregnancy Category D" to Quadramet® (Samarium Sm 153 Lexidronam Injection) is incorrect. Consequently, "Pregnancy Category C" (*... studies in women and animals are not available.*) should be a more proper pregnancy category to be assigned to the above drug.

Therefore, the NIOSH Hazardous Drugs Ccriteria listing for Quadramet® (Samarium Sm 153 Lexidronam Injection) should be revised (see list below).

1. Cancer (carcinogenicity): --
2. Preg Cat (teratogenicity or other developmental toxicity): C
3. Repro Tox (reproductive toxicity): NT
4. Organ Tox (organ toxicity at low doses): (blank)
5. Geno Tox (genotoxicity): --

In accordance with the above revised "rating", Quadramet® (Samarium Sm 153 Lexidronam Injection) should be placed in the list of the "New FDA Drugs and Warning Not Fitting NIOSH Criteria for Hazardous Drugs 2006" similar to various other drugs with comparable NIOSH assessment outcomes that are placed in the above "Not Fitting" list.

In summary, neither Metastron™ (Strontium-89 Chloride Injection) nor Quadramet® (Samarium Sm 153 Lexidronam Injection) possesses the same characteristic of a hazardous drug that is listed in the "New FDA Drugs and Warning NOT Fitting NIOSH Criteria for Hazardous Drugs 2006." Additionally, each of these two radiopharmaceuticals is supplied by the vendor as a finished drug product (stored in a closed vial). Most of the end users obtain the above two radiopharmaceuticals from various commercial nuclear pharmacies in "unit-dose" syringe form ready to be administered to patients. As a result, the risk of direct occupational exposure to either Metastron™ (Strontium-89 Chloride Injection)or Quadramet® (Samarium Sm 153 Lexidronam Injection) should be very insignificant. Thus, I would like to request you to remove both of the aforementioned radiopharmaceuticals from the proposed "hazardous drugs" list.

Once again, I sincerely appreciate the opportunity that your agency has provided to the public in allowing us to express our concerns and comments with regard to the NIOSH alert on hazardous drugs. If you have any questions or require additional information regarding my comments and suggestions as stated above, please feel free to contact me by phone: (507) 284-4104, fax: (507) 266-4461 or e-mail: jhung@mayo.edu. Thank you!

Sincerely yours,

Joseph C. Hung, Ph.D., BCNP
Professor of Pharmacy & Professor of Radiology
Director of Nuclear Pharmacy Laboratories and PET Radiochemistry Facility

Enclosures:

1. Edited Excel file PublicReviewForm2006-05-01-07.xls
2. Attachment 1 – package insert of Metastron™ (Strontium-89 Chloride Injection)
3. Attachment 2 – package insert of Quadramet® (Samarium Sm 153 Lexidronam Injection)

Drugs to Review 2006 Docket #NIOSH-105				Send reviews to: niocindocket@cdc.gov
Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?**		**Comments**
		yes	**no**	
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Abilify	aripiprazole			
Alimta	pemetrexed			
Amevive	alafacept			
Amitiza	lubiprostone			
Apokyn	apomorphine HCl			
Arranon	nelarabine			
Avastin	bevacizumab			
Azilect	rasagiline mesylate			
Baraclude	entecavir			
Chantix	varenicline			
Clolar	clofarabine			
Cordarone	amidarone HCl			
Dacogen	decitibine			
Depacone	valproate Na			
Depakene	valproic acid			
Depakote	divalproex Na			
Depo-Provera**	medroxyprogesterone acetate			
Elidel	pimecrolimus			
Erbitux	cetuximab			
Geodon	ziprasidone			
Gleevec	imatinib mesylate			
Hivid	zalcitibine			
Hycamtin	topotecan HCl			

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Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?** yes	no	**Comments**
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Increlex	mecasermin (rDNA origin)			
Kepivance	palifermin			
Leustatin	cladrabine			
Lunesta	eszopicline			
Lyrica	pregagalin			
Metastron	strontium-89 chloride		√	
Mycamine	micafungin sodium			
Myozyme	alglucosidase alfa			
Nexavar	sorafenib			
Orencia	abatacept			
Paxil	paroxetine HCl			
Pentetate Calcium Trisodium				
Photofrin	porfimer sodium			
Provera**	medroxyprogesterone acetate			
Quadramet	samarium 153 lexidronam		√	
Rapamune	sirolimus			
Revlimid	lenalidomide			
Risperdal Consta**	risperdone			
Risperdal**	risperidone			
Rituxan	rituximab			
Rozerem	ramelteon			
Seroquel	quetiapine fumerate			

Drugs to Review 2006 Docket #NIOSH-105				Send reviews to: niocindocket@cdc.gov
Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?** yes	no	**Comments**
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Spiriva Handihaler	titropium bromide			
Sprycel	dasatinib			
Sustiva	efavirenz			
Sutent	sunitinib malate			
Tarceva	erlotinib HCl			
Tindamax	tinidazole			
Tracleer	bosentan			
Trileptal	oxcarbazepine			
Tygacil	tigcycline			
Tysabri	natalizumab			
Velcade	bortizomib			
Vidaza	azacitidine			
Viramune	nevirapine			
Viread	tenofovir			
Vision Blue	trypan blue			
Zolinza	vorinostat			
Zonegran	zonisamide			
New FDA Drugs and Warnings Not Fitting NIOSH Criteria For Hazardous Drugs				
Actoplus Met	pioglitazone HCl/ metroformin HCl			
Actos	pioglitazone HCl			
Adderall	amphetamines			

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Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?**		**Comments**
		yes	**no**	
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Amphadase**	hyaluronidase			
Apidra	insulin glulisine			
Aptivus	tipranivir			
Aranesp	darbepoetin alfa			
Avandaryl	rosiglitazone maleate/ glimepiride			
Avonex	interferon beta 1a			
Betaseron	interferon beta 1b			
Byetta	exenatide			
Campral	acamprosate calcium			
Cancidis	caspofungin acetate			
ChiRhoStim	human secretion			
Clozaril	clozapine			
Concerta*	methylphenidate HCl			
Cymbalta	duloxetine HCl			
Daytrana*	methylphenidate HCl			
Dexedrine	dextroamphetamine			
Dilaudid	hydromorphone HCl			
Diovan	valsartan			
Elaprase	idursulfate			
Elmiron	pentosan polysulfate Na			
Enablex	darifenacin HBr			
Epogen**	epoetin alfa			

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Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?**		**Comments**
		yes	**no**	
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Eraxis	andulafungin			
Ethyol	amifostine			
Exjade	deferasirox			
Focalin	dexmethyphenidate HCl			
Fortovase**	saquinavir mesylate			
Fosrenol	lanthanum carbonate hydrate			
Gabitril	tiagabine			
Herceptin	trastuzumab			
Humira	adalimumab			
Hydase**	hyaluronidase			
Invirase**	saquinavir mesylate			
Iplex	mecasermin rinfabate			
Januvia	sitagliptin phosphate			
Ketek	telithromycin			
Lamictal	lamotrigine			
Levemir	insulin detemir			
Lucentis	ranibizumab			
Lumigan	bimatoprost			
Macugen	pegaptanib sodium			
Magnevist	gadopentetate dimeglumine			
Metadate*	methyphenidate HCl			
Methylin*	methylphenidate HCl			
Multihance	gadobenate dimeglumine			

Drugs to Review 2006 Docket #NIOSH-105				Send reviews to: niocindocket@cdc.gov
Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?**		**Comments**
		yes	**no**	
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Naglazyme	galsulfase			
Nevanac	nepafenac			
Nexium	esomeprazole magnesuim			
Noxafil	posaconazole			
NutreStore	L-glutamine			
Omacor	omega-3-acid ethylesters			
Opana	oxymorphone HCl			
Pentetate Zinc Trisodium				
Prevacid NapralPAC	lansoprazole; naproxen			
Prezista	darunavir			
Prialt	ziconotide			
Procrit**	epoetin alfa			
Propanolol HCl				
Ranexa	ranolazine			
Raptiva	efalizumab			
Remicade	infliximab			
Ritalin*	methylphenidate HCl			
Sanctura	trospium chloride			
Sensipar	cinacalcet HCl			
Serzone	nefazodone HCl			
Strattera	atmoxetine HCl			
Symlin	pramlintide acetate			

Drugs to Review 2006 Docket #NIOSH-105				Send reviews to: niocindocket@cdc.gov
Reviewer :				
Affiliation :				
Proprietary Name	**Established Name**	**Should this Drug be Included in the NIOSH Hazardous Drugs List ?**		**Comments**
		yes	**no**	
New FDA Drugs and Warnings Fitting NIOSH Criteria For Hazardous Drugs				
Trasylol	aprotinin			
Tyzeka	telbivudine			
Vectibix	panitumumab			
Ventavis	iloprost			
Veregen	kunecatechins			
VESIcare	solifenacin succinate			
Videx	didanosine			
Visudyne	verteporfin			
Vitrase	ovine hyaluronidase			
Wellbutrin**	bupropion HCl			
Xifaxan	rifaximin			
Zarontin	ethosuximide			
Zinecard	dextrazoxane			
Zyban**	bupropion HCl			
Zyprexa	olanzapine			
* = several proprietary names for same drug; ** = two proprietary names for same drug				
ADDITIONAL COMMENTS				

Attachment 1

GE Healthcare

METASTRON
(Strontium-89 Chloride Injection)

R_x ONLY

METASTRON™

(Strontium-89 Chloride injection)

DESCRIPTION

Metastron is a sterile, non-pyrogenic, aqueus solution of Strontium-89 Chloride for intravenous administration. The solution contains no preservative.

Each milliliter contains:

Strontium Chloride	10.9 - 22.6 mg
Water for Injection	q.s. to 1 mL

The radioactive concentration is 37 MBq/mL, 1 mCi/mL, and the specific activity is 2.96-6.17 MBq/mg, 80-167 µCi/mg at calibration. The pH of the solution is 4 - 7.5.

PHYSICAL CHARACTERISTICS

Strontium-89 decays by beta emission with a physical half-life of 50.5 days. The maximum beta energy is 1.463 MeV (100%). The maximum range of β- from Strontium-89 in tissue is approximately 8 mm.

Radioactive decay factors to be applied to the stated value for radioactive concentration at calibration, when calculating injection volumes at the time of administration, are given in Table 1.

Product Code: SMS.2PA

Table 1: Decay of Strontium-89

Day*	Factor	Day*	Factor
-24	1.39	+6	0.92
-22	1.35	+8	0.90
-20	1.32	+10	0.87
-18	1.28	+12	0.85
-16	1.25	+14	0.83
-14	1.21	+16	0.80
-12	1.18	+18	0.78
-10	1.15	+20	0.76
-8	1.12	+22	0.74
-6	1.09	+24	0.72
-4	1.06	+26	0.70
-2	1.03	+28	0.68
0=calibration	1.00		

* Days before (-) or after (+) the calibration date stated on the vial.

CLINICAL PHARMACOLOGY

Following intravenous injection, soluble strontium compounds behave like their calcium analogs, clearing rapidly from the blood and selectively localizing in bone mineral. Uptake of strontium by bone occurs preferentially in sites of active osteogenesis; thus primary bone tumors and areas of metastatic involvement (blastic lesions) can accumulate significantly greater concentrations of strontium than surrounding normal bone.

Strontium-89 Chloride is retained in metastatic bone lesions much longer than in normal bone, where turnover is about 14 days. In patients with extensive skeletal metastases, well over half of the injected dose is retained in the bones.

Excretion pathways are two-thirds urinary and one-third fecal in patients with bone metastases. Urinary excretion is higher in people without bone lesions. Urinary excretion is greatest in the first two days following injection.

Strontium-89 is a pure beta emitter and Strontium-89 Chloride selectively irradiates sites of primary and metastatic bone involvement with minimal irradiation of soft tissues distant from the bone lesions. (The maximum range in tissue is 8 mm; maximum energy is 1.463 MeV.) Mean absorbed radiation doses are listed under the Radiation Dosimetry section.

Clinical trials have examined relief of pain in cancer patients who have received therapy for bone metastases (external radiation to indexed sites) but in whom persistent pain recurred. In a multi-center Canadian placebo-controlled trial of 126 patients, pain relief occurred in more patients treated with a single injection of Metastron than in patients treated with an injection of placebo. Results are given in the following tables.

Table 2 compares the percentage and number of patients treated with Metastron or placebo who had reduced pain and no increase in analgesic or radiotherapy re-treatment.

Table 2: Comparison of the effects of Strontium-89 and placebo, as adjunct to radiotherapy, on treatment outcome over time.

	Months Post-Treatment					
	1	2	3	4	5	6
Metastron	71.4%	78.9%	60.6%	59.3%	36.4%	63.6%
	(n=42)	(n=38)	(n=33)	(n=27)	(n=22)	(n=22)
Placebo	61.4%	57.1%	55.9%	25.0%	31.8%	35.0%
	(n=44)	(n=35)	(n=34)	(n=24)	(n=22)	(n=20)

At each visit, treatment success, defined as a reduction in a patient's pain score without any increase in analgesic intake and without any supplementary radiotherapy at the index site, was more frequent among patients assigned to Metastron than to placebo.

Table 3 compares the number and percentage of patients treated with Metastron or placebo as an adjunct to radiotherapy who were pain free without analgesic at the intervals shown.

Table 3: Comparison of the effects of Strontium-89 and placebo, as adjunct to radiotherapy, on reduction of pain score and analgesic score to zero.

	Months Post-Treatment						
	1	2	3	4	5	6	9
Metastron	6	5	5	3	4	4	2
	14.3%	13.2%	15.2%	11.1%	18.2%	18.2%	18.2%
	(n=42)	(n=38)	(n=33)	(n=27)	(n=22)	(n=22)	(n=11)
Placebo	3	3	2	0	1	1	0
	6.8%	8.6%	5.9%		4.5%	5%	
	(n=44)	(n=35)	(n=34)	(n=24)	(n=22)	(n=20)	(n=17)

The number of patients classified at each visit as treatment successes who were pain free at the index site and required no analgesics was consistently higher in the Metastron group.

New pain sites were less frequent in patients treated with Metastron.

In another clinical trial, pain relief was greater in a group of patients treated with Metastron compared with a group treated with non-radioactive strontium-88.

INDICATIONS AND USAGE

Metastron (Strontium-89 Chloride Injection) is indicated for the relief of bone pain in patients with painful skeletal metastases.

The presence of bone metastases should be confirmed prior to therapy.

CONTRAINDICATIONS

None known.

WARNINGS

Use of Metastron in patients with evidence of seriously compromised bone marrow from previous therapy or disease infiltration is not recommended unless the potential benefit of the treatment outweighs its risks. Bone marrow toxicity is to be expected following the administration of Metastron, particularly white blood cells and platelets. The extent of toxicity is variable. It is recommended that the patient's peripheral blood cell counts be monitored at least once every other week. Typically, platelets will be depressed by about 30% compared to pre-administration levels. The nadir of platelet depression in most patients is found between 12 and 16 weeks following administration of Metastron. White blood cells are usually depressed to a varying extent compared to pre-administration levels. Thereafter, recovery occurs slowly, typically reaching pre-administration levels six months after treatment unless the patient's disease or additional therapy intervenes.

In considering repeat administration of Metastron, the patient's hematologic response to the initial dose, current platelet level and other evidence of marrow depletion should be carefully evaluated.

Verification of dose and patient identification is necessary prior to administration because Metastron delivers a relatively high dose of radioactivity.

Metastron may cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while receiving this drug, the patient should be apprised of the potential hazard to the fetus. Women of childbearing potential should be advised to avoid becoming pregnant.

PRECAUTIONS

Metastron is not indicated for use in patients with cancer not involving bone. Metastron should be used with caution in patients with platelet counts below 60,000 and white cell counts below 2,400.

Radiopharmaceuticals should only be used 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.

Metastron, like other radioactive drugs, must be handled with care and appropriate safety measures taken to minimize radiation to clinical personnel.

In view of the delayed onset of pain relief, typically 7 to 20 days post injection, administration of Metastron to patients with very short life expectancy is not recommended.

A calcium-like flushing sensation has been observed in patients following a rapid (less than 30 second injection) administration.

Special precautions, such as urinary catheterization, should be taken following administration to patients who are incontinent to minimize the risk of radioactive contamination of clothing, bed linen and the patient's environment.

Metastron is excreted primarily by the kidneys. In patients with renal dysfunction, the possible risks of administering Metastron should be weighed against the possible benefits.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Data from a repetitive dose animal study suggests that Strontium-89 Chloride is a potential carcinogen. Thirty-three of 40 rats injected with Strontium-89 Chloride in ten consecutive monthly doses of either 250 or 350 µCi/kg developed malignant bone tumors after a latency period of approximately 9 months. No neoplasia was observed in the control animals. Treatment with Strontium-89 Chloride should be restricted to patients with well documented metastatic bone disease.

Adequate studies with Strontium-89 Chloride have not been performed to evaluate mutagenic potential or effects on fertility.

Pregnancy: Teratogenic effects.

Pregnancy Category D. See Warnings section.

Nursing Mothers

Because Strontium acts as a calcium analog, secretion of Strontium-89 Chloride into human milk is likely. It is recommended that nursing be discontinued by mothers about to receive intravenous Strontium-89 Chloride. It is not known whether this drug is excreted in human milk.

Pediatric Use

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

ADVERSE REACTIONS

A single case of fatal septicemia following leukopenia was reported during clinical trials. Most severe reactions of marrow toxicity can be managed by conventional means.

A small number of patients have reported a transient increase in bone pain at 36 to 72 hours after injection. This is usually mild and self-limiting, and controllable with analgesics. A single patient reported chills and fever 12 hours after injection without long-term sequelae.

DOSAGE AND ADMINISTRATION

The recommended dose of Metastron is 148 MBq, 4 mCi, administered by slow intravenous injection (1-2 minutes). Alternatively, a dose of 1.5 - 2.2 MBq/kg, 40-60 µCi/kg body weight may be used.

Repeated administrations of Metastron should be based on an individual patient's response to therapy, current symptoms, and hematologic status, and are generally not recommended at intervals of less than 90 days.

The patient dose should be measured by a suitable radioactivity calibration system immediately prior to administration.

RADIATION DOSIMETRY

The estimated radiation dose that would be delivered over time by the intravenous injection of 37 MBq, 1 mCi of Strontium-89 to a normal healthy adult is given in Table 4. Data are taken from the ICRP publication "Radiation Dose to Patients from Radiopharmaceuticals"-ICRP #53, Vol. 18, No. 1-4, Page 171, Pergamon Press, 1988.

Table 4: Strontium-89 Dosimetry

Organ	mGy/MBq	rad/mCi
Bone Surface	17.0	63.0
Red Bone Marrow	11.0	40.7
Lower Bowel Wall	4.7	17.4
Bladder Wall	1.3	4.8
Testes	0.8	2.9
Ovaries	0.8	2.9
Uterine Wall	0.8	2.9
Kidneys	0.8	2.9

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

The radiation dose hazard in handling Strontium-89 Chloride injection during dose dispensing and administration is similar to that from phosphorus-32. The beta emission has a range in water of about 8 mm (max.) and in glass of about 3 mm, but the bremsstrahlung radiation may augment the contact dose.

Measured values of the dose on the surface of the unshielded vial are about 65 mR/minute/mCi.

It is recommended that the vial be kept inside its transportation shield whenever possible.

HOW SUPPLIED

Metastron is supplied in a 10 mL vial containing 148 MBq, 4 mCi. The vial is shipped in a transportation shield with approximately 3 mm lead wall thickness, package insert, and two therapeutic agent warning labels.

The vial and its contents should be stored inside its transportation container at room temperature 15°-25°C (59°-77°F).

The calibration date (for radioactivity content) and expiration date are quoted on the vial label. The expiration date will be 28 days after calibration. Stability studies have shown no change in any of the product characteristics monitored during routine product quality control over the period from manufacture to expiration.

This radiopharmaceutical is licensed by the Illinois Emergency Management Agency for distribution to persons licensed pursuant to 32 Illinois Adm. Code 330.260 (a) and Part 335 Subpart F.335.5010 or under equivalent licenses of the USNRC or an Agreement State.

NDC 17156-524-01

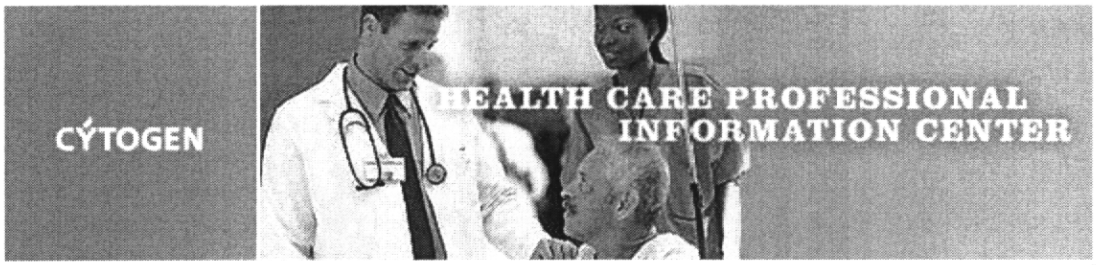
GE Healthcare

Manufactured by:
GE Healthcare Ltd.
Amersham England

GE Healthcare
Medi-Physics, Inc.,
3350 North Ridge Avenue
Arlington Heights, IL 60004

43-9000D Revised February 2006

Attachment 2



QUADRAMET® Prescribing Information

QUADRAMET.
(SAMARIUM SM 153 LEXIDRONAM INJECTION)

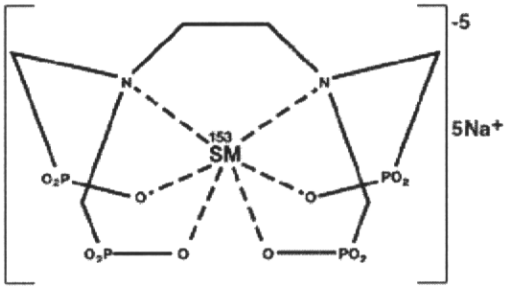
513145-0903 September 2003

Therapeutic – For Intravenous Administration

DESCRIPTION: QUADRAMET® is a therapeutic agent consisting of radioactive samarium and a tetraphosphonate chelator, ethylenediaminetetramethylenephosphonic acid (EDTMP). QUADRAMET® is formulated as a sterile, non-pyrogenic, clear, colorless to light amber isotonic solution of samarium-153 lexidronam for intravenous administration. QUADRAMET® does not contain a preservative.

Each milliliter contains 35 mg EDTMP•H_2O, 5.3 mg Ca [as $Ca(OH)_2$], 14.1 mg Na [as NaOH], equivalent to 44 mg Ca/Na EDTMP (anhydrous calc.), 5-46 µg samarium (specific activity of approximately 1.0-11.0 mCi/µg Sm), and 1850 ± 185 MBq (50 ± 5 mCi) of samarium-153 at calibration.

The structural formula of samarium lexidronam pentasodium is:



The ionic formula is $^{153}Sm^{+3}$ $[CH_2N(CH_2PO_3^{-2})_2]_2$ and the ionic formula weight is 581.1 daltons (pentasodium form, 696).

The pH of the solution is 7.0 to 8.5.

QUADRAMET® is supplied frozen in single-dose glass vials containing 3 mL with 5550 MBq (150 mCi) of samarium-153 at calibration.

Physical Characteristics: Samarium-153 is produced in high yield and purity by neutron irradiation of isotopically enriched samarium Sm 152 oxide ($^{152}Sm_2O_3$). It emits both medium-energy beta particles and a gamma photon, and has a physical half-life of 46.3 hours (1.93 days). 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 - 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 particle energy is 233 keV.

External Radiation: The specific gamma-ray constant for samarium-153 is 0.46 R/mCi-hr at 1 cm (1.24×10^{-5} mSv/MBq- hr at 1 Meter). The half-value thickness of lead (Pb) for samarium-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 in a lead-shielded container and frozen until use.

Radioactive decay factors to be applied to the stated value for radioactive concentration 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	+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

CLINICAL PHARMACOLOGY: QUADRAMET® (samarium Sm-153 EDTMP) has an affinity for bone and concentrates in areas of bone turnover in association with hydroxyapatite. In clinical studies employing planar imaging techniques, more QUADRAMET® accumulates in osteoblastic lesions than in normal bone with a lesion-to-normal bone ratio of approximately 5. The mechanism of action of QUADRAMET® in relieving the pain of bone metastases is not known.

Distribution: Human protein binding has not been studied; however, in dog, rat and bovine studies, less than 0.5% of samarium-153 EDTMP is bound to protein. At physiologic pH, >90% of the complex is present as $^{153}Sm[EDTMP]^{-5}$, and <10% as $^{153}SmH[EDTMP]^{-4}$. The octanol/ water partition coefficient is $<10^{-5}$.

Skeletal Uptake: The greater the number of metastatic lesions, the more 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 65.5% ± 15.5% of the injected dose in 453 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 52 metastatic lesions. If the number of metastatic lesions 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, single species that consists of one atom of the Sm-153 and one molecule of the EDTMP, 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, urine and blood 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 Skeletal 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. Over the first 30 minutes, the radioactivity (mean ± SD) in the blood decreased to 15% (±8%) of the injected dose with a t 1/2 of 5.5 min (±1.1 min). After 30 minutes, the radioactivity cleared from the blood more slowly with a t1/2 of 65.4 min (± 9.6 min). Less than 1% of the dose injected remained in the blood 5 hr 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 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 scintiscans 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 insufficiency have not been studied.

Drug/Drug Interaction

Drug-drug interaction studies have not been studied.

Pharmacodynamics

The beta particle of ^{153}Sm-EDTMP travels an average of 3.1 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 ^{153}Sm-EDTMP uptake is similar to the presence or absence of ^{99m}Tc diphosphonate uptake (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 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 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 visual 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 in oral morphine milligram equivalents.

Of the 270 patients studied, 232 (86%) had prostate cancer and 38 (14%) had other primary cancers. In study A, 80 (68%) of the patients had prostate cancer and 38 (32%) had a variety of other primary tumors. 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, pain (the AUPC) decrease from 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 QUADRAMET® 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]

	STUDY A (n = 73) (b)		STUDY B (n = 150) (c)	
WEEK	Placebo N=36	1.0 mCi/kg N=37	Placebo N=50	1.0 mCi/kg N=100
Baseline	26.5 (11.8)	28.7 (12.3)	28.5 (14.1)	28.1 (12.9)
1	26.1 (10.3)	27.6 (14.1)	27.9 (14.6)	25.8 (13.1)
2	24.4 (10.4)	23.8 (13.7)	28.1 (15.4)	20.6 (13.9)*
3	24.3 (11.0)	20.5 (11.5)*	25.8 (16.1)	20.1 (13.3)*
4	24.7 (12.1)	18.8 (10.8)*	24.7 (15.3)	19.9 (13.7)*

(a) Area Under the Pain Curve (SD).
(b) Excludes 5 patients with missing baseline or extreme values; and all 40 patients who received 0.5 mCi QUADRAMET®. QUADRAMET® 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 the two clinical trials, the patient use of analgesics differed. In Study A, the patients did not receive specific instructions on analgesic reduction. In Study B, patients were encouraged to adjust their pain medication as needed. As shown in Table 4, the morphine equivalent

analgesic use in study A generally increased from baseline 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 use of opioid analgesics, while the QUADRAMET® treated patients decreased their use of opioid analgesics.

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 = 150) (c)	
WEEK	Placebo N=36	1.0 mCi/kg N=37	Placebo N=50	1.0 mCi/kg N=100
Baseline	93.5 (154.0)(a)	127.1 (189.9)	78.4 (83.1)	96.5 (166.6)
1	106.8 (173.8)	125.7 (192.6)	84.5 (91.1)	93.5 (165.5)
2	127.1 (238.4)	144.8 (276.7)	85.6 (90.9)	82.9 (122.9)
3	133.9 (254.0)	146.6 (278.2)	100.1 (119.4)	79.6 (131.2)*
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; 0 = none.
(b) Excludes 5 patients with missing baseline or with extreme values; and all 40 patients who received 0.5 mCi QUADRAMET®. QUADRAMET® 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 48/100 (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 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® causes bone marrow suppression. In clinical trials, white blood cell 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.

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%)	173 (94%)

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 greater than or equal to 4.0 x 10^3µL, and Platelets greater than or equal to150,000/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 are falling or who have other clinical or laboratory findings suggesting DIC. Because of the unknown potential for additive effects on bone marrow, QUADRAMET® should not be given concurrently with chemotherapy or external beam radiation therapy unless the clinical benefits outweigh the risks. Use of QUADRAMET® in patients with evidence of compromised bone marrow reserve from previous therapy or disease involvement is not recommended 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.

Pregnancy: As with other radiopharmaceutical 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 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 potential should be advised to avoid becoming pregnant soon after receiving QUADRAMET®. Men and women patients should be advised to use an effective method of contraception after the administration of QUADRAMET®.

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) developed a variety of electrocardiographic (ECG) changes (with or without the presence of hypocalcemia). The causal relationship between the hypocalcemia and ECG changes has not been studied. Whether QUADRAMET® causes electrocardiographic changes or arrhythmias in humans has not been studied. Caution 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 used 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 7% 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 cancer does not prevent the 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.

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 others in 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 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 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®. 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 2 hours 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 time for 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/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 Fisher 344 rats, at dietary doses up to 100 mg/kg/day (not the maximum tolerated dose). However, at study termination in female Fisher 344 rats, this dose was associated with statistically significantly 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 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 below 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).

Of these patients, 472 (83%) had at least one adverse event. In a subgroup of 399 patients who received QUADRAMET® 1.0 mCi/kg, there were 23 deaths and 46 serious adverse events. The deaths occurred an average of 67 days (9 to 130) after QUADRAMET®. Serious events occurred an average of 46 days (1 - 118) after QUADRAMET®. Although most of the patient deaths and serious adverse events appear to be related to the underlying disease, the relationship of end stage disease, marrow invasion by cancer cells, previous myelotoxic treatment and QUADRAMET® toxicity can not be easily distinguished. In clinical studies, two patients with rapidly progressive prostate cancer developed thrombocytopenia and died 4 weeks after receiving QUADRAMET®. One of the patients showed evidence of disseminated intravascular coagulation (DIC); the other patient experienced a fatal cerebrovascular accident, with a suspicion of DIC. The relationship of the DIC to the bone marrow suppressive effect of Samarium is not known. Marrow toxicity occurred in 277 (47%) patients (See Warnings section).

In controlled studies, 7% of patients receiving 1.0 mCi/kg QUADRAMET® (as compared to 6% of patients receiving placebo) reported a transient increase in bone pain shortly after injection (flare reaction). This was usually mild, self-limiting, and responded to analgesics.

The most common adverse events observed in controlled clinical studies of QUADRAMET®, are given in Table 6.

TABLE 6

SELECTED ADVERSE EVENTS REPORTED IN GREATER THAN OR EQUAL TO 1.0 % OF PEOPLE WHO RECEIVED QUADRAMET® OR PLACEBO IN CONTROLLED CLINICAL TRIALS

ADVERSE EVENT	Placebo	QUADRAMET® 1.0 mCi/kg

	N = 90	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%)
Diarrhea	3 (3.3%)	12 (6.0%)
Nausea &/or Vomiting	37 (41.1%)	65 (32.7%)
Hematologic & Lymphatic	12 (13%)	54 (27%)
Coagulation Disorder	0	3 (1.5%)
Hemoglobin 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 (2.0%)
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 (2.0%)
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 hemorrhage (gastrointestinal, ocular) reported in <1%.

In an additional 200 patients who received QUADRAMET® in uncontrolled clinical trials, adverse events that were reported at a rate of greater than or equal to 1.0% were similar except for 9 (4.5%) patients who had agranulocytosis. Other selected adverse events that were reported in <1% of the patients who received QUADRAMET® 1.0 mCi/kg in any clinical trial include: alopecia, angina, congestive heart failure, sinus bradycardia, and vasodilation.

OVERDOSAGE: Overdosage with QUADRAMET® has not been reported. An antidote for QUADRAMET® overdosage is not known. The anticipated complications of overdosage would likely be secondary to

bone marrow suppression from the radioactivity of ^{153}Sm, or secondary to hypocalcemia and cardiac arrhythmias related to the EDTMP.

DOSAGE AND ADMINISTRATION: The recommended dose of QUADRAMET® is 1.0 mCi/kg, administered intravenously over a period of one minute through a secure in-dwelling catheter and followed with a saline flush. Dose adjustment in patients 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 radioisotope 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 often as possible after injection to minimize radiation exposure to the bladder.

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 contain molecules 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 received QUADRAMET®. Although electron emissions from ^{153}Sm 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 localize.

When blastic osseous 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 Surfaces	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
QUADRAMET® is supplied frozen in a single-dose 10 mL glass vial containing 1850 ± 185 MBq/mL (50 ± 5 mCi/mL) of samarium-153, at calibration.

QUADRAMET® is available in the following size:

NDC# 50419-209-03 3mL fill size with total activity of 5550 MBq (150mCi).

The vial is shipped in a lead shield; a package insert is included.

The drug product expires 48 hours after the time of calibration noted on the label, or 8 hours after thawing, whichever is earlier.

STORAGE: Store frozen at -10° to -20°C in a lead shielded 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 120.500 for the uses listed in 105 CMR 120.537 or under equivalent licenses of the U.S. Nuclear Regulatory Commission, an Agreement State or a Licensing State.

THIS PRODUCT
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