

## SCIENTIFIC DISCUSSION

**This module reflects the initial scientific discussion and scientific discussion on procedures, which have been finalised before 1 April 2003. For scientific information on procedures after this date please refer to module 8B.**

### 1. Introduction

The active substance in Quadramet is samarium [ $^{153}\text{Sm}$ ] lexidronam pentasodium INN, i.e.  $^{153}\text{Sm}$  complexed with EDTMP (ethylenediaminetetramethylenephosphonic acid), also referred to as  $^{153}\text{Sm}$ -EDTMP.

The clinical indication for Quadramet relates to the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases. In this therapeutic context there are other radiopharmaceuticals, which are authorised with similar indications, e.g.  $^{32}\text{P}$  and  $^{89}\text{Sr}$ , although Quadramet has been developed in an attempt to utilise several advantages over these radioisotopes. For example,  $^{153}\text{Sm}$  has a shorter physical half-life than  $^{89}\text{Sr}$ , which has a half-life of 50 days and which also has a slow onset of pain relief and a prolonged myelosuppressive effect. A potential benefit of samarium [ $^{153}\text{Sm}$ ]-EDTMP in comparison with  $^{32}\text{P}$  is its lower beta energy and lack of incorporation into normal metabolic pathways.

$^{153}\text{Sm}$  itself has a half-life of 46.3 hours, emits  $\beta$ -radiation with therapeutic properties and  $\gamma$ -radiation whose energy allows its visualisation by  $\gamma$ -camera. The ligand EDTMP is a tetrakisphosphate chelator with a high affinity for skeletal tissue and concentrates in areas with high metabolic turn-over in intimate association with hydroxyapatite.

Therefore as expected, Sm-EDTMP has a high uptake in bone, low uptake in soft tissue and rapid excretion of non-localised activity via the urine. However, the ligand also has affinity for free calcium in the plasma, and in order to counteract this effect, the formulation of Quadramet contains added calcium. This is considered to be safer without changing the biodistribution of the product. At pH above 6 all of the calcium is bound to EDTMP and does not significantly contribute to the plasma free calcium pool on injection of the product.

The proposed dose of  $^{153}\text{Sm}$ -EDTMP in the indication is 37 MBq per kg body weight (1 mCi/kg), equivalent to 1.4 mg/kg of Ca/Na-EDTMP. The product is to be administered by slow intravenous injection through an established intravenous line over a period of one minute (intravenous bolus). Repeat dose administration should be based on an individual patient's response to prior treatment and on clinical symptoms. A minimum interval of 8 weeks should be allowed between doses, subject to recovery of adequate bone marrow function.

In a relevant patient population for the proposed indication (prostatic and breast cancer with skeletal metastases and bone pain) with relevant efficacy end-points Quadramet in a dose of 1 mCi/kg resulted in pain relief in approximately 60-65% of treated patients with a median duration of 3-4 months.

The risk benefit ratio is considered to be favourable, and in addition, the rapid urinary excretion of the radioactivity should be of benefit both to the patient and the environment.

### 2. Chemical, pharmaceutical and biological aspects

#### Active substance

Samarium [ $^{153}\text{Sm}$ ] lexidronam pentasodium INN, equivalent to approx. 20-46  $\mu\text{g}/\text{ml}$  samarium

#### Pharmaceutical development:

The company in the dossier outlined the ideal characteristics of a radiotherapeutic bone agent and the reasons behind the choice of isotope and chelating agent were discussed. It is clear that the nuclear properties of  $^{153}\text{Sm}$  make it suitable for use in radiotherapy.

An initial prototype preparation consisted of  $^{153}\text{Sm}$ -Na-EDTMP, i.e. as the sodium salt only. However, the chelating properties of EDTMP produced a reduction in blood calcium levels and led to

the development of a  $^{153}\text{Sm}$ -Ca/Na-EDTMP complex which, due to the presence of added calcium in the formulation, prevented the fall in plasma calcium levels and was therefore considered to be safer. The addition of calcium to the formulation reduces the potential toxicity of the formulation in this regard without changing the biodistribution.

### **Method of preparation**

The finished product is manufactured by mixing filtered samarium [ $^{153}\text{Sm}$ ] chloride solution with filter-sterilised Ca/Na-EDTMP solution for several minutes followed by dispensing and autoclaving at  $121^\circ\text{C}$ . Batch size is adjusted according to orders. In-process controls are applied to radioactive concentration, volume and a check on autoclave parameters.

In general, process validation and in-process control measures should provide an adequate assurance of sterility and compliance with specification. During manufacture, filter integrity testing is performed before and after filtration by the bubble point method and bioburden limits prior to filtration are controlled at a limit in compliance with current European guidelines.

Batch results show satisfactory consistency within specifications.

### **Packaging materials:**

Vials and stoppers are washed with purified water. Vials are sterilised in the oven at  $250^\circ\text{C}$  for at least 60 minutes, stoppers are autoclaved at  $121^\circ\text{C}$  for at least 20 minutes.

This provides adequate assurance of sterility.

### **Control of active substance and other starting materials**

Samarium [ $^{153}\text{Sm}$ ]-EDTMP is not isolated as such. Structural analysis studies (NMR- $^1\text{H}$ , NMR- $^{13}\text{C}$ , FAB-MS, energy dispersive analysis, elemental analysis, gravimetric analysis and titration) have been carried out on the nonradioactive samarium complex and later compared to  $^{153}\text{Sm}$ -EDTMP, sodium salt with identical results. The samarium-EDTMP complex consists of one atom of samarium quantitatively chelated by one molecule of EDTMP. At pH above 6 all of the calcium is bound to EDTMP and does not significantly contribute to the plasma free calcium pool on injection of the product.

Impurities have been synthesised and HPLC retention times and relative response factors determined. Studies show that high levels of radiolytic impurities have no effect on biodistribution of the  $^{153}\text{Sm}$ -EDTMP complex, and furthermore the presence of degradants of EDTMP results in no change in the radiochemical purity of the product. The affinity of samarium is greater for EDTMP than for the degradation products. Toxicity studies have been performed on a preparation containing high levels of degradation products.

### **$^{153}\text{SmCl}_3$ solution**

Specifications and routine tests include radionuclidic identity and purity, samarium content and radioactive concentration. The relative amount of radionuclidic impurities varies with duration of irradiation of the initial samarium oxide target. Nuclear transformations leading to the isotope and radionuclidic impurities ( $^{152}\text{Eu}$ ,  $^{154}\text{Eu}$  and  $^{156}\text{Eu}$ ) have been studied and the impact on dosimetry has been reliably estimated.

### **EDTMP.H<sub>2</sub>O**

Suitable information has been given on the preparation and control of this material. A satisfactory validated assay is performed, and the determination of impurities by  $^{31}\text{P}$ -NMR has also been validated.

Two potential related substances have been identified although these appear at levels below the limit of reliable quantification and present no toxicological significance for the finished product.

#### **(a) Packaging material**

The immediate packaging consists of PhEur type I glass vials and teflon-coated chlorobutyl/natural rubber stoppers, which comply with the PhEur monograph for rubber closures.

## **Control tests on the finished product**

Analytical methods have been described and validated, and the specification has been improved during the review process.

The samarium complex is identified chromatographically and radionuclidic identity is adequately established. Concerning radionuclidic purity, the applicant has proposed a satisfactory specification, although they have also promised to keep the specification for gamma-contaminants under review in the light of large scale batch experience.

Radiochemical purity is established as  $\geq 99\%$ .

The radioactive concentration limits are defined as 1300 MBq/ml  $\pm 10\%$  at calibration.

The specification is completed by microbiological tests and tests for chemical impurities, and is considered to characterise the product in a way that should indicate uniform and consistent performance *in vivo*.

## **Stability**

### **General Comment**

Radiation emanating from the  $^{153}\text{Sm}$  induces radiolytic degradation of the EDTMP ligand in addition to those impurities arising from preparation of the active substance and product. These related impurities have been identified.

### **Active substance**

Studies under long term and accelerated conditions have indicated no changes except a small increase in impurity content. Seen in connection with the pronounced degradation of EDTMP in the finished product, the limits for impurities in the active substance are acceptable. A satisfactory retest period has been established.

### **Finished product**

Five batches have been studied. As expected, the content of EDTMP decreased, both during the 4 days and the 6 hours, accompanied by a corresponding increase in the amount of chemical impurities. A slight decrease was also seen in pH (max 0.5 pH unit).

Regarding container compatibility there were no differences in pH, radiochemical purity and radioactive concentration whether stored in the upright or upside down position.

The company has committed itself to reassess the shelf-life specifications when results from industrial scale batches are available.

Based on these stability studies, the product is distributed frozen in dry ice and should be stored frozen at  $-10$  to  $-20^\circ\text{C}$  by the user, in the original packing. It should be used within 6 hours of thawing and should not be refrozen after thawing. The applicant claims that low-temperature storage reduces radiolytic degradation products and there is acceptable evidence for this claim.

Proposed limits for related impurities in the product have been justified and qualified by toxicology studies described in Part III of the dossier, carried out on artificially-degraded material having a comparable impurity profile to the product in therapeutic use.

In general, the shelf-life and storage conditions cited in the SPC are considered to be justified.

### **GMP statement**

See section II.1 of this report.

### 3. Overview of part III of the dossier: toxico-pharmacological aspects

An Expert Report, Textual Summaries, Tabulated Summary Reports and literature references or study reports, adequately supports the marketing application. All pivotal safety studies were conducted in GLP compliance, and in general the documentation was of good quality.

Studies describing the non-clinical pharmacology and toxicology of samarium [ $^{153}\text{Sm}$ ]-EDTMP, have utilised a non-radioactive formulation of Sm-EDTMP as either the sodium salt (Sm-Na-EDTMP) or the calcium/sodium salt (Sm-Ca/Na-EDTMP). The use of a non-radioactive formulation in the examination of pharmacological and toxicological effects is justified because

- 1) high doses are generally required to elucidate the total pharmacologic and toxicologic profile of a new agent, by using a radioactive formulation in such high doses, the effect of the radioactivity would overshadow all other pharmacologic and toxicologic effects; and
- 2)  $^{153}\text{Sm}$ -EDTMP is present in a very small concentration compared to the other components of the clinical formulation.

The  $^{153}\text{Sm}$ -EDTMP complex was selected on the basis of its high tropism for bone, like all phosphonic acid complexes, but also because of its high blood clearance, fast urinary excretion and absence of metabolism. Strong, fast bone uptake occurs with a lesion-to-normal bone uptake ratio of the order of 5. Over 50% is taken up in 30 minutes with the free fraction being rapidly eliminated by the urinary route preventing soft tissue uptake. In the preparation, the complex is present at a relatively low level since there is an excess of Ca/Na-EDTMP. For this reason, some of the toxicological and pharmacological studies were conducted with EDTMP or the sodium or sodium/calcium salt thereof.

#### Pharmacodynamics

##### Pharmacodynamic effects relating to the proposed clinical indication

In one study, dogs with a variety of skeletal neoplasias, mainly osteogenic sarcomas located on distal radius, were treated with  $^{153}\text{Sm}$ -EDTMP. The data indicate

- a good response in primary lesions with marked ossification,
- in general, small lesions with little lysis and metastatic lesions responded well to treatment,
- periosteal and cortical lesions were less sensitive.
- a poor response of treatment from large lesions showing little calcification,

Based on the study it can be considered that chelate uptake by bone tissue is important for clinical efficacy; large tumours may have areas that are not fully exposed to the short-penetrating  $\beta$ -radiation resulting in less efficacy, as compared to small tumour sites.

#### Safety Pharmacology

Data on the effects on the skeletal system and the cardiovascular system have been submitted. Other organ systems (kidney, CNS and respiratory) have been addressed in the single and repeated dose toxicity studies, as well as in the pharmacodynamic (re. the proposed indication) section.

Effects encountered were expected on the basis of chemical and structural properties of  $^{153}\text{Sm}$ -EDTMP; i.e., in animals, treatment-related interferences were observed on the mineralisation processes in bone and in the phosphorus/calcium metabolism.

The Na-Sm-EDTMP complex appeared to induce dose-dependent fall in blood pressure in anaesthetised dogs at i.v. bolus doses as low as 0.3 mg/kg, deaths were encountered at 20 mg/kg. Higher i.v. infusion doses (20-30 mg/kg) in anaesthetised dogs induced decrease in blood pressure and tachycardia. In the conscious dog, 10 and 20 mg/kg induced no change in blood pressure or heart rate; only at 30 mg/kg was a transient increase in heart rate observed. ECG recordings revealed a T-wave inversion at low doses ( $\geq 3$  mg/kg), then an increase in the PR and QT-intervals with a decrease in P- and R-wave amplitude. No ECG recordings were conducted in conscious dogs.

Further comparative studies for cardiovascular safety were conducted with the Na and Ca/Na salts of EDTMP and showed dose-related falls in ionised calcium and magnesium for both salts. It was

demonstrated that the Ca/Na salt form had a better safety profile, as compared to the Na salt. Gross pathological examination revealed no treatment-related effects on the cardiovascular system. Thus, these data provide a reasonable rationale for the development of the Ca/Na salt form, and indicate that (very) high doses by rapid intravenous bolus injection may cause cardiovascular effects secondary to calcium chelation.

### **Drug Interactions**

Concomitant administration of melphalan and  $^{153}\text{Sm}$ -EDTMP potentiated toxicity in the rat. This potentiation was not observed if administration of the drugs was separated by a 5-day interval. However, additional studies in mice and rats indicated that interaction with melphalan has no direct relevancy for the proposed clinical use of  $^{153}\text{Sm}$ -EDTMP.

### **Pharmacokinetics**

Single dose kinetic studies were performed in the rat and in the rabbit. No repeated dose administration studies were performed, on the grounds that the medicinal product is intended for single dose use only. Protein-binding studies were described in the dossier.

Distribution studies in the rat, rabbit, dog and monkey have been evaluated, and urine from these animals was analysed in biotransformation studies.

During development of the product, pharmacokinetic studies have been performed mainly with the Na-formulation. However, a comparative biodistribution study of Na and Ca/Na-formulation showed no significant differences between these two formulations in terms of biolocalisation at either 2 or 72 hours after intravenous administration in the rat.

A variety of ligands were evaluated in animal studies. Of the  $^{153}\text{Sm}$  complexes evaluated, the one that gave the best overall combination of high uptake in bone with little or no accumulation in any soft tissue was the complex formed with EDTMP. Two hours post injection into rats, 58% of the injected dose was localised to the skeleton with only 0.2% in the liver. Elimination was equally extensive from other soft tissues with only 0.03% remaining in the entire blood volume at the two hour timepoint.

In general, the data demonstrate that  $^{153}\text{Sm}$ -EDTMP has high affinity for bone, i.e., it localises to growing areas of bone matrix, specifically the layer of osteoid undergoing mineralisation, and that samarium is always associated with calcium and phosphorus in highly mineralised zones. The data demonstrate that fast urinary elimination of the administered fraction not undergoing bone uptake occurs resulting in a rapid blood clearance. The exposure of soft tissues is very limited, and transient. Although limited documentation exists, it appears that  $^{153}\text{Sm}$ -EDTMP is not metabolised. This is in agreement with what is known in relation to other phosphonates. This pharmacokinetic profile emphasises the important role of the renal function in the clearance process, and it is suggested that injected activity of  $^{153}\text{Sm}$ -EDTMP should be adjusted with regard to renal function. Renal failure reduces the urinary elimination of radioactivity and increases soft tissue uptake. In general the pharmacokinetic profile supports the clinical use, i.e., the specific accumulation at the site of action and the rapid blood clearance limiting the potential toxicity.

### **Toxicology**

Data relating to single and repeated dose toxicity have been evaluated in the rat, mouse and dog.

The symptomatology of acute toxicity of  $^{153}\text{Sm}$ -EDTMP can be related to the chelating properties of EDTMP. Signs of acute toxicity in rats and mice include ataxia, tremors and convulsions.

Target organs were the phosphorus/calcium metabolism and the kidneys.

The adverse effect on the phosphorus/calcium metabolism is considered related to the chelating properties of the EDTMP complex. Points for consideration in this regard may include the concentration of the solution and the speed of administration, however, the clinical data do not suggest that this is a safety issue in human therapeutic use taken into account the proposed pharmaceutical composition and the proposed method of administration.

The degradation products, as described above, cause the treatment-induced adverse effects on the kidney. Kidney lesions were observed in single dose toxicity studies in mice and rats at high doses of  $^{153}\text{Sm}$ -EDTMP containing degradation products.

Repeated dose toxicity studies in dogs helped characterising the kidney lesions. Data from dogs given repeated doses of  $^{153}\text{Sm}$ -EDTMP enriched with degradation products for one month, established a NOAEL of 2.5 mg/kg/day. This NOAEL is difficult to extrapolate to the human situation because the posology differed from the one proposed for clinical use (repeated daily administration for 1 month as compared to single dose (or repeated dose every 8th week) administration in humans). However, the NOAEL from this study does demonstrate a high margin of safety, (also supported by data from the clinical trials).

No Reproduction toxicity studies have been performed. Therefore, the SPC has appropriate contraindications and restrictions.

### **Mutagenic- and oncogenic/carcinogenic potential**

Non-radioactive Sm-EDTMP with or without degradation products showed no mutagenic potential in a battery of in vitro and in vivo test systems. One weakness of the documentation is, however, that no test systems were exposed to  $^{153}\text{Sm}$ -EDTMP enriched with degradation products. However, this is not considered to be a major safety issue for three reasons: 1) the product is radioactive *per se*, 2) the target human population should be taken into consideration, and 3) the fact that the test systems were exposed to at least some degree of degradation products.

### **Local Tolerance**

Rabbit studies indicate that accidental perivenous administration should be avoided during clinical use because of the risk for producing hematoma. The proposed method of administration in the SPC, i.e. intravenous through an established intravenous line, appears to adequately diminish this risk.

### **Effects related to the radioactivity of $^{153}\text{Sm}$**

The only adverse pharmacological effect attributable to administration of  $^{153}\text{Sm}$ -EDTMP is reversible bone marrow suppression; this is the same safety profile as observed in man. Data in dogs indicate an adequate safety margin following single dose administration (single administration of 30 mCi/kg was well tolerated). The data indicate a cumulative bone marrow toxicity after repeated administration because in one study (0.5, 1 or 2 mCi/kg), longer time to normalisation (6 weeks) after 4 repeated administrations occurred, as compared to time to normalisation after a single dose administration (3-4 weeks), and, in another study (1 mCi/kg), bone marrow depression lasted somewhat longer following two doses than after one. Because convincing human data on cumulative bone marrow toxicity is somewhat lacking, it is reasonable that these findings in the dog should be included in the SPC text. This should emphasise the importance of blood count monitoring in patients, especially when administration is repeated.

It should be noted that despite the radiation effects on the bone marrow and the secondary changes in the haematological profiles, no episodes of infection or bleeding were recorded preclinically. Further, it was noted that at the very high radioactive exposure levels of the bone marrow in the preclinical studies, the potential for effective regeneration still persists.

In conclusion, the data obtained in dogs is in agreement with the human data, i.e., secondary dose-related, reversible hematotoxicity caused by pharmacologically induced bone marrow depression was the primary target of toxicity. Gender-specificity has not been examined in animals.

### **Summary of toxic-pharmacological aspects**

Repeat dose toxicity studies in the rat revealed the kidney as the target organ with histopathological changes including nephrosis, tubular dilatation and vacuolar degeneration, which persisted throughout a 4-week drug-free recovery period. Adverse renal effects also occurred in the dog, with evidence of reversibility upon cessation of treatment. The other major finding was haematological, characterised by decreased haematocrit and haemoglobin with evidence of reversibility. In view of the proposed therapeutic indication these findings are not an impediment to the grant of a Marketing Authorisation.

No reproductive toxicity studies have been conducted. Due to the radioactivity the drug is contraindicated in pregnant women since it is considered to present a risk to the foetus. The same applies for lactating mothers, although excretion of the product in breast milk has not been investigated.

The ‘cold’ product with and without degradation products was non-genotoxic. However, due to the radioactivity of the samarium isotope, the product obviously presents a genotoxic hazard. Its use is acceptable in view of the proposed clinical indication.

Carcinogenicity studies are not required for this product. Nevertheless EDTMP was evaluated in 2 rat studies in which there was evidence of carcinogenicity (pancreatic islet cell adenomas and carcinomas in the dietary study, osteosarcoma in the oral gavage study). The aetiology of these findings was unknown. They did not present an impediment to the grant of a Marketing Authorisation in view of the proposed clinical indication.

#### 4. Clinical aspects

Like other phosphonic acid complexes, samarium [<sup>153</sup>Sm]-EDTMP has an affinity for skeletal tissue and concentrates in areas of bone turnover in intimate association with hydroxyapatite.

The core clinical development programme consisted of the following studies:

Study BA-xxx	Volume Ref	Type of Study	Doses mCi/kg	Doses	N =	Design
101*	1	Clinical  Pharmacol.	2 mCi total*	SD	5	Pilot, open
102	1		0.1 - 1.0	SD/R D	22	Dose-ranging, open
103	2		1.0 - 3.0	SD	52	Dose-ranging, open
104	3		0.5 - 1.0	RD	19	Open, Max Tol Dose
105	5		1.0, 1.5, 2.0	SD	23	Open
107	7		0.5, 1.0	RD	22	Open
109	8		0.5	SD	7	Dosimetry
108	11	Pivotal	0.5 vs 1.0	SD	114	SB, Randomised, PG
106/110	17	Efficacy	P vs 0.5 vs 1.0	SD	118	DB, Randomised, PG
Sm10/11	28	Studies	P vs 1.0	SD	141	DB, Randomised, PG
Sm12	39	Miscellaneous	1.0	SD	18	Open, compassionate use, long-term

\* = In study BA-101, patients were given a total dose of 2 mCi (and not on per kg basis)

P = Placebo

SD = Single dose,

RD = Repeat dose

SB = Single blind

DB = Double blind

PG = Parallel Group

#### Pharmacodynamics & Pharmacokinetics

Samarium [<sup>153</sup>Sm] - EDTMP was shown to localise to bone. It has a favourable bone to soft tissue and lesion to normal bone localisation ratio. 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. Thus, areas of metastatic involvement can accumulate significantly greater amounts of Quadramet than surrounding normal bone.

Scintiscans revealed that except for the bladder, selective concentration of the activity in the body could only be seen in the skeleton on both whole body and spot images.

Ratio of Uptake	<sup>153</sup> Sm-EDTMP	<sup>99m</sup> Tc-HDP
<b>Lesion to Normal Bone</b>	4.04 ± 2.62	4.01 ± 1.97
<b>Lesion to Soft Tissue</b>	5.98 ± 3.18	6.87 ± 4.67
<b>Normal Bone to Soft tissue</b>	2.47 ± 1.01	2.44 ± 1.25

There was no accumulation of activity in any non-osseous tissue.

In patients, Quadramet is rapidly cleared from the blood. It is rapidly cleared from the blood into urine and the lesional tissue. Total skeletal uptake of Quadramet in studies of 453 patients with a variety of primary malignancies was  $65.5 \pm 15.5\%$  of the administered dose. Urinary excretion occurred predominantly during the first 4 hours. At 12 hours,  $35.3 \pm 13.6\%$  of the administered dose had been excreted into the urine. In view of the  $\beta$ -emission from samarium [<sup>153</sup>Sm]-EDTMP and its target organ dosimetry, the most significant secondary effects are on bone marrow.

Administration of 1.0 mCi/kg dose was considered to be optimal on the basis of pain score, use of analgesics and myelotoxicity.

#### Therapeutic efficacy

The applicant has submitted three well-conducted Phase III pivotal studies to provide the principal evidence of efficacy and safety in the proposed indication. These are:

BA-108, BA-106/110 and 424Sm10/11

In these three studies, 288 patients received the active drug and 85 received the placebo.

Patients included had confirmed histological diagnosis of malignancy and of metastatic lesions in bone (as evidenced by pain overlying at least one site of enhanced uptake on <sup>99m</sup>Tc bone scan).

- BA 108: Single-blind, comparative between doses, multicentre, parallel group, randomised study of 114 patients with bone metastases from various types of malignancies.  
75M + 39F, mean age 63yr (range 20-83)  
16 weeks total (Single-blind phase was 4 weeks)  
Single dose of 0.5 mCi/kg or 1 mCi/kg
- BA 106/110: Double-blind, 3-arm comparative ( vs placebo & 2 doses ), multicentre, parallel groups, randomised study of 118 patients with bone metastases from various malignancies.  
91M + 27F, mean age 63.5yr (range 24-83)  
16 weeks total (Double-blind phase was 4 weeks)  
Single dose of 0.5 mCi/kg or 1 mCi/kg or placebo
- 424Sm10/11: Double-blind, placebo-controlled, multicentre, parallel group, randomised study of 141 patients with hormone refractory bone metastases from prostate carcinoma (stage D2)  
mean age 71yr (range 46-86)  
16 weeks total (Double blind phase was 4 weeks)  
Single dose of 1 mCi/kg or placebo

Three pivotal studies provide evidence of efficacy. The MA applicant has confirmed that the studies were conducted according to GCP standards.



## Primary Endpoints of Efficacy

Visual Analogue Scale (VAS)	(BA 108, BA 106/110, 424Sm10/11)
Pain Descriptor Scale (PDS)	(424Sm10/11)
Analgesic Use (AUPC)	(BA 108, BA 106/110, 424Sm10/11)
Physician's Global Assessment (PGA)	(BA 108, BA 106/110)

## Results

### BA 108

An analysis of the changes from baseline in the AUPC and PGA results demonstrates that samarium [<sup>153</sup>Sm]-EDTMP at doses of 0.5 mCi/kg and 1.0 mCi/kg provides relief from pain associated with osteoblastic bone metastases. The effect is greater and statistically significant at 1.0 mCi/kg dose level.

However, even at this dose level, there was no obvious trend correlating decrease in AUPC and a decrease in use of opioid analgesics. The onset of pain relief is apparent in evaluations performed at 2 weeks after drug administration. In those who have responded by week 4, the relief persists for 12 weeks in more than half. The benefit was particularly evident for breast cancer patients, at week 4 on a dose of 1.0 mCi/kg dose.

### BA 106/110

Analysis of the changes from baseline in AUPC and the PGA results demonstrate that samarium [<sup>153</sup>Sm]-EDTMP at doses of 0.5 mCi/kg and 1.0 mCi/kg provides relief from pain associated with osteoblastic bone metastases. The effect is greater and statistically significant at 1.0 mCi/kg dose level. The interval to onset of pain relief depends on the parameter by which it is evaluated but it is apparent in most evaluations performed at 3 weeks after drug administration. The effect persists at least until week 16 in some individuals on this dose.

### 424Sm10/11

This study provides the most convincing evidence on efficacy. Analysis of the changes from baseline in VAS-AUPC and PDS-AUPC, together with a demonstrable decrease in the mean opioid analgesic use among the patients in the active treatment group suggests that samarium [<sup>153</sup>Sm]-EDTMP at doses of 1.0 mCi/kg provides relief from pain associated with osteoblastic bone metastases. The effect is independent of opioid use. The difference between placebo and the active drug was significant by week 1 (PDS-AUPC) and by week 2 (VAS-AUPC). The median time to onset of pain relief was 1 week and the median duration of this relief was 4 weeks.

## Safety

578 patients represented by provide the safety database:

- 85 receiving placebo in controlled studies
- 288 receiving samarium [<sup>153</sup>Sm] - EDTMP in comparative studies
- 205 receiving samarium [<sup>153</sup>Sm] - EDTMP in open studies

Death was reported in 70 (12%) of the 578 patients in the clinical trials programme. Of these, 43 were in the three comparative studies and 27 in other (all uncontrolled) studies. There were 5 deaths on placebo (5.9%) and 65 deaths on samarium [<sup>153</sup>Sm]-EDTMP (13.1%). According to the investigators this was not linked to Quadramet. The cause of death in 65 of the 495 patients receiving samarium [<sup>153</sup>Sm] - EDTMP was:

Progression of disease:	27
Progressive disease plus other factors	7
Cardiopulmonary causes	14
Deaths where thrombocytopenia is mentioned	2
Deaths where DIC was mentioned	3
Deaths where cord compression mentioned	3
Deaths where bleeding mentioned	3
Suicide	1
Aspiration of stomach contents	1
Cause unknown	4

The main toxic effect is myelotoxicity but the data confirm that this is readily reversible. The data also suggests that the frequency and severity of myelotoxicity are less than that following administration of other radionuclides currently available for the proposed indication.

The intensity of myelotoxicity of samarium [ $^{153}\text{Sm}$ ] - EDTMP is categorised by the National Cancer Institute Common Toxicity Grades as follows:

<b>Toxicity Grade</b>	<b>Haemoglobin (g/100ml)</b>	<b>Total WBC (Giga/l)</b>	<b>Granulocytes (Giga/l)</b>	<b>Platelets (Giga/l)</b>
<b>0</b>	≥ 11	≥ 4.0	≥ 2.0	≥ 100
<b>1</b>	9.5 - 10.9	3.0 - 3.9	1.5 - 1.9	75 - 99
<b>2</b>	8.0 - 9.4	2.0 - 2.9	1.0 - 1.4	50 - 74
<b>3</b>	6.5 - 7.9	1.0 - 1.9	0.5 - 0.9	25 - 49
<b>4</b>	< 6.5	< 1.0	< 0.5	< 25

The overall frequency of myelotoxicity in the three pivotal studies was as follows:

<b>Parameter</b>	<b>Toxicity Grade</b>	<b>Control (n=80)</b>	<b>0.5 mCi/kg (n=86)</b>	<b>1.0 mCi/kg (n=180)</b>
<b>Haemoglobin</b>	0-2	73 (91%)	76 (88%)	160 (89%)
	3	6 (8%)	10 (12%)	17 (9%)
	4	1 (1%)	0	3 (2%)
<b>Platelets</b>	0-2	80 (100%)	80 (93%)	168 (93%)
	3	0	3 (3%)	10 (6%)
	4	0	3 (3%)	2 (1%)
<b>WBC</b>	0-2	80 (100%)	81 (94%)	164 (92%)
	3	0	5 (6%)	15 (8%)
	4	0	0	0

At a dose level of 1.0 mCi/kg, the mean nadir values are as follows:

WBC	about 3600/ $\mu$ l
Platelets	about 127000/ $\mu$ l
Haemoglobin	about 10 g/dl

The nadir values for WBC and platelets are not at levels that would be associated with infectious or haemorrhagic complications.

The mean times to nadir at a dose level of 1.0 mCi/kg are:

For WBC	3-4 weeks
For platelets	4 weeks
For haemoglobin	7 weeks

A total of 18 patients in the three pivotal studies cited at the beginning of the safety chapter of this report developed a total of 25 severe reactions, possibly or probably associated with samarium [ $^{153}\text{Sm}$ ]-EDTMP. The most frequent were anaemia (11), leucopenia (2) and pain (2).

The overall number of patients who discontinued because of adverse events was 30 (5%) of the 578 patients. Of these, 2 were in the placebo group and the rest on the active treatment. The main events in the active treatment group were as follows:

Cord/root compression	11	
Haemotoxicity	6 *	
Anaemia	2 *	* = considered to be drug-related
Renal complications	3	

When compared to placebo, the only events reported more frequently with samarium [ $^{153}\text{Sm}$ ] - EDTMP included :

Pain	Flare
Nausea and vomiting	Urinary tract infection
Diarrhoea	Infection

and other events mentioned in the SPC.

### Conclusion on clinical aspects

Concerning efficacy, the data generated by the studies summarised above support the conclusions that:

1. Quadramet given by slow intravenous injection is effective in relieving pain from bone metastasis.
2. A dose of 1.0 mCi/kg of Quadramet is significantly more effective than placebo.
3. Approximately 55% to 65% of patients experience pain relief at 4 weeks after receiving 1.0 mCi/kg of Quadramet.
4. Following administration of Quadramet at a dose of 1.0 mCi/kg, the onset of pain relief is apparent by week 1 or week 2 and the duration of relief is at least 8 weeks (mean duration 3-4 months).

Concerning safety, a detailed evaluation of the observations on cord/root compression was performed and this issue has been addressed in the SPC under Section 4.8, Undesirable Effects, together with effects relating to haemotoxicity and anaemia. Initial data suggesting an increased mortality with Quadramet treatment were further analysed. The applicant presented the deaths in randomised trials in a manner which allowed a variety of more reliable calculations to be made. For example the death rate among patients who were exposed to placebo at any time (a criterion comparable to that used for Quadramet exposure) was 11.8%, compared to 13.1% in patients exposed to Quadramet. This reanalysis confirmed that there was no evidence of any relationship between death rate and dose of Quadramet. Clinically, there were no toxic effects on the renal function in patients with normal function at baseline; however, the safety in patients with impairment of renal function is unknown.

Therefore treatment with Quadramet should be adjusted with regard to renal function as proposed by the applicant in the SPC.

## **5. Conclusions**

The CPMP considered that the Marketing Authorisation application contained appropriate pharmaceutical data as well as preclinical and clinical information to meet quality, safety and efficacy standards, and consensus was reached to support the Marketing Authorisation of Quadramet in the following therapeutic indication:

Quadramet is indicated for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases, which take up technetium [ $^{99m}\text{Tc}$ ]-labelled biphosphonates on bone scan. The presence of osteoblastic metastases which take up [ $^{99m}\text{Tc}$ ]-labelled biphosphonates should be confirmed prior to therapy.