SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Quadramet 1.3 GBq/mL solution for injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each mL of solution contains 1.3 GBq of samarium (^{153}Sm) lexidronam pentasodium at the reference date (corresponding to 20 to 80 µg/mL of samarium per vial).

Samarium specific activity is approximately 16 – 65 MBq/µg of samarium.

Each vial contains 2-4 GBq at the reference date.

Samarium-153 emits both medium-energy beta particles and an imageable gamma photon, and has a radioactive half-life of 46.3 hours (1.93 days). 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.

Excipient with known effect: sodium 8.1 mg/mL.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear, colourless to light amber solution with pH ranging between 7.0 and 8.5.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Quadramet is indicated for the relief of bone pain in patients with multiple painful osteoblastic skeletal metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates on bone scan.

The presence of osteoblastic metastases which take up technetium (^{99m}Tc)-labelled bisphosphonates must be confirmed prior to therapy.

4.2 Posology and method of administration

Quadramet should only be administered by physicians experienced in the use of radiopharmaceuticals and after full oncological evaluation of the patient by qualified physicians.

Posology
The recommended activity of Quadramet is 37 MBq per kg body weight.

Renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Paediatric population
Quadramet is not recommended for use in children and adolescents below the age of 18 years due to a lack of data on safety and efficacy.

Method of administration
For single use only.
Quadramet is to be administered by slow intravenous route through an established intravenous line
over a period of one minute. Quadramet should not be diluted before use.

Patients who respond to Quadramet generally experience the onset of pain relief within 1 week after
treatment. Relief of pain may persist for 4 weeks up to 4 months. Patients who experience a reduction
in pain may be encouraged by their physician to decrease their use of opioid analgesics.

Repeat administration of Quadramet should be based on an individual patient's response to prior
treatment and on clinical symptoms. A minimum interval of 8 weeks should be respected, subject to
recovery of adequate bone marrow function.

The data on the safety of repeated dosing are limited and based on compassionate use of the product.

For instructions on preparation of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

4.3 Contraindications

- Hypersensitivity to the active substance (ethylenediaminetetramethylenephosphonate (EDTMP)) or similar phosphonates or to any of the excipients listed in section 6.1.
- Pregnancy (See section 4.6).
- Patients having received chemotherapy or hemi-body external radiation therapy in a preceding period of 6 weeks.
- Concomitant use with myelotoxic chemotherapy (see section 4.5)

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification
For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required therapeutic effect.

In patients with evidence of compromised bone marrow reserve from previous therapy or disease involvement, the use of Quadramet is not recommended unless the potential benefit of the treatment outweighs its risks.

Renal impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible.

Paediatric population
For information on the use in paediatric population see section 4.2. Careful consideration of the indication is required since the effective dose per MBq is higher than in adults.

It should not be used concurrently with other bisphosphonates if an interference is shown on the technetium (^{99m}Tc)-labelled bisphosphonate bone scans.

Myelosuppression
Treatment of patients with compromised bone marrow function is not recommended. Complete Blood Counts should be obtained within 2 weeks prior to the start of therapy. The following thresholds should be considered prior to initiating therapy:

- Haemoglobin <100 g/L
- Total white cell count $<5 \times 10^9$/L
- Absolute neutrophil count $<2 \times 10^9$/L
- Platelet count $<100 \times 10^9$/L

Patient preparation
The patient should be encouraged to ingest (or receive by intravenous administration) a minimum of 500 mL of fluids prior to injection and should be encouraged to void as often as possible after injection to minimise radiation exposure to the bladder.

Patients with urinary problems (obstruction or incontinence) should be catheterised after administration to minimise the risk of radioactive contamination of clothing, bed linen, and the patient's environment. Patients' release has to be aligned with local regulations.

The clearance of Quadramet being rapid, the precautions relating to the excreted urinary radioactivity has to be aligned with local regulations.

After the procedure
Close contact with infants and pregnant women should be restricted during 48 hours.

Because of potential bone marrow suppression after administration, blood counts should be monitored weekly for at least 8 weeks, beginning 2 weeks after administration of Quadramet, or until recovery of adequate bone marrow function.

Specific warnings
This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially 'sodium free'.

Paravenous injection must be avoided due to the risk of local tissue necrosis. Injection should be strictly intravenous to avoid local deposit and irradiation. In the event of paravenous injection, the injection should be immediately stopped and the site of injection should be warmed and rested in elevated position. When radiation necrosis occurs, surgical intervention may be necessary.

4.5 Interaction with other medicinal products and other forms of interaction

Because of the potential for additive effects on bone marrow, the treatment should not be given concurrently with chemotherapy or external beam radiation therapy. Quadramet may be given subsequent to either of these treatments after allowing for adequate marrow recovery.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient. The possibility of pregnancy must strictly be ruled out.

Contraception
Women of childbearing potential and men have to use effective contraception after the administration and the whole period of follow-up.

Pregnancy
The use of samarium (^{153}Sm) lexidronam pentasodium is contraindicated in pregnant women (see section 4.3).

Breast-feeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding.

There are no available clinical data relating to the excretion of Quadramet in human milk. If the administration is considered necessary, formula feeding should be substituted for breast-feeding and the expressed feeds discarded.

Close contact with infants should be restricted during 48 hours.

Fertility
No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

Quadramet may have a minor influence on the ability to drive and use machines

4.8 Undesirable effects

Summary of the safety profile
In clinical studies in individuals who received Quadramet, the most frequently reported reactions were thrombocytopenia, anaemia and leukopenia.
The most important serious adverse reactions associated with Quadramet are disseminated intravascular coagulation, bone marrow failure, hypersensitivity, anaphylactic reaction, intracranial haemorrhage, cerebrovascular accident and spinal cord compression.

Tabulated list of adverse reactions
The following table subsumes the observed reaction types and symptoms sorted by System Organ Class. The frequencies listed below are defined using the following convention:
Very common (≥ 1/10); common (≥ 1/100 to <1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); very rare (< 1/10,000); not known (cannot be estimated from the available data).

Table 2: Adverse Reactions from clinical trials and post marketing surveillance

System Organ Class	Frequency	Adverse reactions
Blood and lymphatic system disorders	Very Common	Thrombocytopenia[2] Anaemia[2] Leukopenia[2]
	Uncommon	Disseminated intravascular coagulation[2] Bone marrow failure [2]
Immune system disorders	Not known	Hypersensitivity[1] Anaphylactic reaction[1]
Metabolism and nutrition disorders	Uncommon	Anorexia
Nervous system disorders	Uncommon	Haemorrhage intracranial Cerebrovascular accident [2] Spinal cord compression [2]
	Common	Dizziness
Gastrointestinal disorders	Common	Nausea
	Uncommon	Vomiting
	Not known	Diarrhoea[1]
Skin and subcutaneous tissue disorders	Uncommon	Hyperhidrosis
Musculoskeletal and connective tissue disorders	Common	Bone pain [2]
General Disorders and administration site conditions	Common	Asthenia

[1] Adverse reactions from spontaneous reporting
[2] See section Description of selected adverse reactions

Description of selected adverse reactions

Post marketing reports of thrombocytopenia have included isolated reports of intracranial haemorrhage, and cases in which the outcome was fatal.

Decreases in white blood cell and platelet counts and anaemia were observed in patients receiving Quadramet.

In clinical trials white blood cell and platelet counts decreased to a nadir of approximately 40 % to 50 % of baseline 3 to 5 weeks after a dose, and generally returned to pre-treatment levels by 8 weeks post treatment.

The few patients who experienced Grade 3 or 4 hematopoietic toxicity usually either had a history of recent external beam radiation therapy or chemotherapy or had rapidly progressive disease with probable bone marrow involvement.

A small number of 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.

A few patients experienced cord/root compressions, disseminated intravascular coagulation and cerebrovascular accidents. The occurrence of these events may be linked to the patients' disease evolution. When there are spinal metastases at the cervico-dorsal level, an increased risk of spinal cord compression cannot be excluded.

The radiation dose resulting from therapeutic exposure may result in higher incidence of cancer and mutations. In all cases, it is necessary to ensure that the risks of the radiation are less than from the disease itself. The effective dose is 798 mSv when the maximal recommended activity for a 70 kg weight patient of 2600 MBq is administered.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme - Website: www.mhra.gov.uk/yellowcard - or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

In the event of administration of a radiation overdose with Quadramet the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Various pain palliation radiopharmaceuticals.
ATC Code: V10BX02

Mechanism of action
Quadramet has an affinity for skeletal tissue and concentrates in areas of bone turnover in intimate association with hydroxyapatite.

Pharmacodynamic effects
Studies in rats have demonstrated that Quadramet is cleared rapidly from the blood and localises to growing areas of bone matrix, specifically the layer of osteoid undergoing mineralisation.

Clinical efficacy and safety
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.

5.2 Pharmacokinetic properties

Distribution
In patients, Quadramet is rapidly cleared from the blood. Thirty minutes after injection of the agent to 22 patients, only 9.6 ± 2.8 % of the administered activity remained in plasma. At 4 and 24 hours, plasma radioactivity had decreased from 1.3 ± 0.7 % to 0.05 ± 0.03 %.

Organ uptake
Total skeletal uptake of Quadramet in studies of 453 patients with a variety of primary malignancies was 65.5 ± 15.5 % of the administered activity. A positive correlation was found between skeletal uptake and the number of metastatic sites. In contrast, skeletal uptake was inversely proportional to plasma radioactivity at 30 minutes.

Elimination
Urinary excretion occurred predominantly during the first 4 hours (30.3 ± 13.5 %). At 12 hours, 35.3 ± 13.6 % of the administered activity had been excreted into the urine. Less urinary excretion occurred in patients who had extensive bony metastases, regardless of the amount of radiopharmaceutical administered.

Biotransformation
Analysis of urine samples found the radioactivity to be present as the intact complex.

Renal impairment
The pharmacokinetics in patients with renal impairment has not been characterised.

5.3 Preclinical safety data

The radiolysis products of Sm-EDTMP showed a renal toxicity in rats and dogs with a no effect level of 2.5 mg/kg.

Repeated dose administration of samarium (^{153}Sm)-EDTMP to dogs indicated a slightly longer time for depressed bone marrow and peripheral haematological parameters to recover when compared to recovery following only single dose administration.

Radioactive Sm-EDTMP has not been tested for mutagenicity/carcinogenicity but due to the radiation dose resulting from therapeutic exposure it should be regarded as presenting a genotoxic/carcinogenic risk.

Non-radioactive Sm-EDTMP showed no mutagenic potential in a battery of *in vivo* and *in vitro* tests. The same results were observed for Sm-EDTMP enriched with radiolysis degradants.

In a carcinogenic potential study of EDTMP, osteosarcomas occurred in rats at high doses. In the absence of genotoxic properties, these effects can be assigned to the EDTMP chelatant properties leading to osseous metabolism disturbances.

No studies have been performed to assess the effect of Quadramet on reproduction.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Total EDTMP (as EDTMP.H_2O)
Calcium-EDTMP sodium salt (as Ca)
Total sodium (as Na)
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with the other medicinal products.

6.3 Shelf-life

1 day from the activity reference time stated on the label.

Use within 6 hours of thawing. After thawing, do not freeze again.

6.4 Special precautions for storage

Quadramet is delivered frozen in dry ice.
Store in a freezer at -10°C to -20°C in the original package.
For storage conditions after thawing of the medicinal product, see section 6.3.

Storage of radiopharmaceuticals should be in accordance with national regulation on radioactive materials.

6.5 Nature and contents of container

15 mL colourless European Pharmacopoeia Type I drawn glass vial closed with Teflon-coated chlorobutyl/natural rubber stopper and aluminium flip-off overseal.

Each vial contains 1.5 mL (2 GBq at reference time) to 3.1 mL (4 GBq at reference time) of solution for injection.

6.6 Special precautions for disposal

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses of the competent official organisation.

Radiopharmaceuticals should be prepared in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

For instructions on preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product, the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting etc.

The preparation is likely to result in a relatively high radiation dose to most patients. The administration of Quadramet may result in significant environmental hazard. This may be of concern to the immediate family of those individuals undergoing treatment or the general public depending on the level of activity administered.

Suitable precautions in accordance with national regulations should be taken concerning the activity eliminated by the patients in order to avoid any contaminations.
Quadramet may contains 154-Eu with a half-life of 8.5 years which will be retained in the skeleton after Quadramet therapy. This should be taken into account for the disposal of radioactive waste and when Radiation Alarm Systems are activated.

7. MARKETING AUTHORISATION HOLDER

CIS bio international
Boîte Postale 32
F-91192 GIF-SUR-YVETTE Cedex
FRANCE

8. MARKETING AUTHORISATION NUMBER

PLGB 11876/0024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10. DATE OF REVISION OF THE TEXT

22/01/2026

11. DOSIMETRY (IF APPLICABLE)

The estimated absorbed radiation doses to an average adult patient from an intravenous injection of Quadramet are shown in Table 3. The dosimetry estimates were based on clinical biodistribution studies using methods developed for radiation dose calculations by the Medical Internal Radiation Dose (MIRD) Committee of the Society of Nuclear Medicine.

Because Quadramet is excreted in the urine, radiation exposure was based on a urinary voiding interval of 4.8 hours. Radiation dose estimates for bone and marrow assume that radioactivity is deposited on bone surfaces, in accordance with autoradiograms of bone samples taken from patients who received Quadramet.

TABLE 3: RADIATION ABSORBED DOSES	
Organ	**Absorbed dose per injected activity (mGy/MBq)**
Adrenals	0.009
Brain	0.011
Chest	0.003
Gallbladder	0.004
Ascending colon wall	0.005
Descending colon wall	0.010
Small intestine	0.006
Myocardial wall	0.005
Kidneys	0.018
Liver	0.005
Lungs	0.008
Muscle	0.007
Ovaries	0.008
Pancreas	0.005
Red marrow	1.54
Bone surfaces	6.76
Skin	0.004
Spleen	0.004
Stomach	0.004
Testes	0.005
Thymus	0.004
Thyroid	0.007
Urinary bladder wall	0.973
Uterus	0.011
Effective dose (mSv/MBq)	0.307

The effective dose resulting from the administration of an activity of 2 600 MBq for an adult weighting 70 kg is about 798 mSv.

Radiation dose to specific organs, which may not be the target organ of therapy, may be influenced significantly by pathophysiological changes induced by the disease process. This should be taken into consideration when using the following information.

For an administered activity of 2 600 MBq for an adult weighting 70 kg, the typical radiation dose to the target organ, skeletal metastases, is 86.8 Gy and the typical radiation doses to the critical organs are: normal bone surfaces 17.6 Gy, red marrow 4.0 Gy, urinary bladder wall 2.5 Gy, kidneys 0.047 Gy and ovaries 0.021 Gy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Allow the product to thaw at room temperature before administration.

The solution for injection should be visually inspected before use. It should be clear without particles. The operator should be careful to protect the eyes while inspecting the solution for clarity.

The activity should be measured by a dose calibrator immediately before administration. Verification of the dose to be administered and patient identification are necessary prior to administration of Quadramet.

Withdrawals should be performed under aseptic conditions. The vial must never be opened. After disinfection of the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.

If the integrity of this vial is compromised, the product should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.