Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

OSTEOCIS 3mg kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3mg of sodium oxidronate (or hydroxymethylene diphosphonate, HMDP)

The radionuclide is not part of the kit.

Excipient with known effect:
Each vial contains 4.5 mg of sodium.

For the full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
White pellet.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution the solution of technetium (^{99m}Tc) oxidronate obtained is indicated for bone scintigraphy, where it delineates areas of altered osteogenesis.

4.2 Posology and method of administration

This medicinal product is intended for use in designated nuclear medicine facilities only, and should only be handled by authorised personnel.

Posology

Adults and elderly population
The average activity administered by single intravenous injection is 500 MBq (300 - 700 MBq) for an adult weighting 70 kg. Other activities may be justifiable. There is no special dosage regimen for the elderly patient.
Renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Patients with high bone uptake and/or severe renal impairment
A dose adjustment can be required.

Paediatric population
The use in children and adolescents has to be considered carefully, based upon clinical needs and assessing the risk/benefit ratio in this patient group.
The activities to be administered to children and to adolescents may be calculated according to the recommendations of the Paediatric Task Group of the EANM (2008). This activity can be calculated from the formula below using a multiplying coefficient based on the patient's body mass (table 1).

Recommended activity [MBq] = 35 MBq x Factor (Table 1)

Table 1

Body weight	factor	Body weight	factor	Body weight	factor
3 kg	= 1*	22 kg	= 5.29	42kg	= 9.14
4 kg	= 1.14*	24 kg	= 5.71	44kg	= 9.57
6 kg	= 1.71	26 kg	= 6.14	46kg	= 10.00
8 kg	= 2.14	28 kg	= 6.43	48kg	= 10.29
10 kg	= 2.71	30 kg	= 6.86	50kg	= 10.71
12 kg	= 3.14	32 kg	= 7.29	52-54kg	= 11.29
14 kg	= 3.57	34 kg	= 7.72	56-58kg	= 12.00
16 kg	= 4.00	36 kg	= 8.00	60-62kg	= 12.71
18 kg	= 4.43	38 kg	= 8.43	64-66kg	= 13.43
20 kg	= 4.86	40 kg	= 8.86	68kg	= 14.00

*In very young children (up to 1 year) a minimum dose of 40 MBq is necessary in order to obtain images of sufficient quality.

Method of administration:

This medicinal product should be reconstituted before administration to the patient.
The radiolabelled solution is administered by a single intravenous injection.

For instructions on extemporaneous preparation of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.

Image acquisition

Images obtained shortly after injection (e.g. in the so-called 3-phase bone scan procedure) will only partly reflect metabolic bone activity. Late phase static scintigraphy should be performed not earlier than 2 hours after injection.

4.3 Contraindications

Hypersensitivity to the active substance (diphosphonates), to any of the excipients listed in section 6.1 or to any of the components of the labeled radiopharmaceutical.

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 diagnostic information.

An interval of at least 2 days must be observed between any previous scintigraphy with other technetium (^{99m}Tc)-labelled agents and administration of technetium (^{99m}Tc-)- oxidronate.

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Renal impairment

Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible (see section 11).

Patients with high bone uptake and/or severe renal impairment

Careful consideration of the indication is required since an increased exposure is possible in these patients. This must be taken into account when calculating the activity to be administered (see section 11).

Paediatric population

For information on the use in paediatric population, see section 4.2.
In infants and children particular attention should be paid to the relatively higher radiation exposure of the epiphyses in growing bone.
Careful consideration of the indications is required since the effective dose per MBq is higher than in adults (see section 11)

Patient preparation

The patient should be well-hydrated before the start of the examination and urged to void before scanning and as often as possible during the first hours after the study in order to reduce radiation to the bladder wall

To avoid accumulation of tracer in the musculature it is advised that strenuous exercise be discouraged immediately after injection until satisfactory bone imaging has been effected.

Inadvertent or accidental subcutaneous administration of technetium (^{99m}Tc) oxidronate should be avoided as perivascular inflammation has been described.

After the procedure
Close contact with infants and pregnant women should be restricted during 4 h.

Specific warnings

This medicinal product contains 4.5 mg of sodium per vial. Depending on the time when you administer the injection, the content of sodium given to the patient may in some cases be greater than 1 mmol (23 mg) per dose. This should be taken into account in patients in low sodium diet.

Precautions with respect to environmental hazard are in section 6.6.

4.5 Interaction with other medicinal products and other forms of interactions

The accumulation of technetium (^{99m}Tc) oxidronate in the skeleton, and thus the quality of the scintigraphic procedure, may be decreased after medication with:
- chelates,
- diphosphonates,
- tetracycline or
- iron containing drugs.

Regular medication with aluminium containing drugs (notably antacids) may lead to abnormal high accumulation of technetium (^{99m}Tc) in the liver, presumably caused by formation of labelled colloids.

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 any) should be offered to the patient.

Pregnancy

Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus. Only essential investigations should therefore be carried out during pregnancy, when the likely benefit far exceeds the risk incurred by mother and foetus.

Administration of 700 MBq technetium (^{99m}Tc) oxidronate to a patient with normal bone uptake results in an absorbed dose to the uterus of 4.41 mGy. The dose decreases to 2.03 mGy in patients with high bone uptake and/or severely impaired kidney function.

Breastfeeding

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 and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, one breast feed should be banked prior to injection and the subsequent one discarded after injection. Breast feeding can be restarted 4 hours post injection.
Close contact with infants should be restricted during this period.

4.7 Effects on ability to drive and use machines

Osteocis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following table presents how the frequencies are reflected in this section:

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)

In this table the undesirable effects are classified in accordance with the MedDRA SOCs.

MedDRA Body system SOCs	**Preferred term**	**Frequency**
Immune system disorders	Anaphylactoid reaction	Very rare
Vascular disorders	Hypotension	Very rare
Gastro-intestinal disorders	Nausea	Very rare
Skin and subcutaneous tissue disorders	Rash	Very rare
Musculoskeletal and connective tissue disorders	Arthralgia	Very rare

Adverse drug effects are extremely rare following administration of technetium (^{99m}Tc) oxidronate injection. Reports suggest an incidence of not more than one in 200,000 administrations. Symptoms of anaphylactoid reactions are rash, nausea, hypotension and sometimes arthralgia. Onset of symptoms may be delayed 4 to 24 hours after administration.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects.
As the effective dose equivalent is 5.6 mSv when the maximal recommended activity of 700 MBq is administered these adverse events are expected to occur with a low probability.

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 HPRA Pharmacovigilance
Website: www.hpra.ie

4.9 Overdose

In the event of the administration of a radiation overdose with technetium [^{99m}Tc] oxidronate 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: radiopharmaceutical preparation for diagnostic use
ATC code:V09BA01

At the chemical concentrations used for diagnostic examinations, technetium (^{99m}Tc) oxidronate does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

Distribution
Intravenously administered technetium (^{99m}Tc) oxidronate is rapidly distributed throughout the extracellular space.

Organ uptake
Skeletal uptake begins almost immediately and proceeds rapidly. 30 minutes post injection 10% of the initial dose is still present in whole blood. At 1 hour, 2 hours, 3 hours and 4 hours after injection these values are resp. 5%, 3%, 1.5% and 1%.

Elimination
Clearance from the body takes place via the kidneys. Of the administered activity about 30% is cleared within the first hour, 48% within two hours and 60% within 6 hours.

5.3 Preclinical safety data

Toxicological studies with rats have demonstrated that with a single intravenous injection of 30 mg/kg no deaths were observed. Minimal liver abnormalities were seen at this dose level. Toxicity with repeated administration of 10 mg/kg/day over 14 days in rats was not observed. In the dog, after repeated administration of 3 and 10 mg/kg/day over 14 days, histological changes in the liver (microgranuloma) were observed together with long-lasting indurations at the site of injection. This agent is not intended for regular or continuous administration.

Mutagenicity studies, toxicity to reproduction and development studies and long-term carcinogenicity studies have not been carried out.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride dihydrate
Ascorbic acid
Sodium chloride
Sodium hydroxide (pH adjustment)
Under nitrogen atmosphere

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.

6.3 Shelf life

1 year.
The expiry date is indicated on the outer packaging and on each vial.
After radiolabelling, do not store the labelled product above 25°C and use within 8 hours.

6.4 Special precautions for storage

Store the kit at 2°C - 8°C (in a refrigerator).

For storage conditions after radiolabelling, see section 6.3.

Storage for radiopharmaceuticals should be in accordance with national regulations on radioactive materials.

6.5 Nature and contents of container

15ml, colourless, European Pharmacopoeia type I, drawn glass vials, closed with chlorobutyl rubber stoppers and aluminium caps.

Pack sizes: Kit of 5 multidose vials.

6.6 Special precautions for disposal and other handling

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 licences of the competent official organisation.

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

Content of the vial is intended only for use in the preparation of technetium (^{99m}Tc) oxidronate and is not administered directly without first undergoing the preparative procedure.

For instructions on extemporaneous 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 minimize risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporaneous preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc) injection is added, adequate shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

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

7 MARKETING AUTHORISATION HOLDER

CIS bio International
BP 32
91192 Gif-Sur-Yvette Cedex
France

8 MARKETING AUTHORISATION NUMBER

PA0677/007/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first Authorization : 26th May 2000

Date of next renewal : 26th May 2010

10 DATE OF REVISION OF THE TEXT

11 DOSIMETRY

For this product the effective dose equivalent resulting from an administered activity of 700 MBq is typically 5.6 mSv (per 70 kg individual).

For an administered activity of 700 MBq the typical radiation dose to the target organ (bone) is 44.1 mGy and the typical radiation dose to the critical organ (bladder wall) is 35 mGy.

In cases of high bone uptake and/or severely impaired kidney function, the effective dose equivalent resulting from an administered activity of 700 MBq of technetium (^{99m}Tc) oxidronate is 5.7 mSv. The typical radiation dose to the target organ is 84 mGy and the typical radiation dose to the critical organ (red marrow) is 12.6 mGy.

(^{99m}Tc) technetium disintegrates with the emission of gamma radiation with an energy of 140 keV and a half-life of 6 hours to (^{99}Tc) technetium which can be regarded as quasi stable.
The dosimetry data were quoted from ICRP Publication 53 for phosphonates.

Radiation exposure (normal bone uptake)
as absorbed dose / injected activity (mGy/MBq)

Organ	**Adult**	**Children (age in years)**			
		15	**10**	**5**	**1**
Adrenals	0.0019	0.0027	0.0039	0.0060	0.011
Bladder wall	0.050	0.062	0.090	0.13	0.24
Bone surface	0.063	0.082	0.13	0.22	0.53
Breast	0.00088	0.00088	0.0014	0.0022	0.0042
Stomach wall	0.0012	0.0015	0.0025	0.0037	0.0070
Small intestine	0.0023	0.0028	0.0044	0.0066	0.012
Upper large intestine	0.0020	0.0025	0.0038	0.0062	0.011
Lower large intestine	0.0038	0.0047	0.0072	0.010	0.017
Kidneys	0.0073	0.0089	0.013	0.018	0.033
Liver	0.0013	0.0016	0.0024	0.0038	0.0070
Lungs	0.0013	0.0016	0.0024	0.0036	0.0069
Ovaries	0.0035	0.0046	0.0066	0.0097	0.016
Pancreas	0.0016	0.0020	0.0030	0.0046	0.0085
Red marrow	0.0096	0.013	0.020	0.038	0.075
Spleen	0.0014	0.0018	0.0028	0.0043	0.0081
Testes	0.0024	0.0033	0.0055	0.0084	0.016
Thyroid	0.0010	0.0016	0.0022	0.0035	0.0056
Uterus	0.0061	0.0076	0.012	0.017	0.028
Other tissue	0.0019	0.0023	0.0033	0.0050	0.0089
Effective dose equivalent (mSv/MBq)	0.0080	0.010	0.015	0.025	0.050

Radiation exposure (high bone uptake and/or severely impaired kidney function)
as absorbed dose / injected activity (mGy/MBq)

Organ	**Adult**	**Children (age in years)**			
		15	**10**	**5**	**1**
Adrenals	0.0035	0.0050	0.0072	0.011	0.021
Bladder wall	0.0025	0.0035	0.0054	0.0074	0.015
Bone surface	0.12	0.16	0.26	0.43	1.0

Breast	0.0021	0.0021	0.0032	0.0051	0.0096
Stomach wall	0.0026	0.0032	0.0051	0.0073	0.014
Small intestine	0.0031	0.0038	0.0057	0.0085	0.016
Upper large intestine	0.0029	0.0036	0.0053	0.0086	0.015
Lower large intestine	0.0034	0.0042	0.0065	0.0096	0.018
Kidneys	0.0030	0.0037	0.0056	0.0087	0.016
Liver	0.0027	0.0033	0.0049	0.0075	0.014
Lungs	0.0030	0.0037	0.0053	0.0081	0.015
Ovaries	0.0029	0.0041	0.0059	0.0089	0.016
Pancreas	0.0032	0.0040	0.0059	0.0089	0.016
Red marrow	0.018	0.023	0.037	0.072	0.14
Spleen	0.0026	0.0034	0.0051	0.0078	0.015
Testes	0.0023	0.0027	0.0039	0.0060	0.011
Thyroid	0.0024	0.0037	0.0054	0.0083	0.014
Uterus	0.0029	0.0037	0.0054	0.0082	0.015
Other tissue	0.0030	0.0036	0.0053	0.0081	0.015
Effective dose equivalent (mSv/MBq)	0.0082	0.011	0.017	0.028	0.061

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must never be opened. The solutions 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.

Method of the preparation of technetium (^{99m}Tc) oxidronate

OSTEOCIS is to be used after reconstitution by the addition of sterile, pyrogen-free, isotonic sodium pertechnetate (^{99m}Tc) injection, allowing the preparation of technetium (^{99m}Tc) oxidronate Injection.

Sodium pertechnetate (^{99m}Tc) injection should comply with European Pharmacopoeia specifications.

Usual precautions regarding sterility and radioprotection should be respected.

Take a vial from the kit and put it in an appropriate lead shielding.

Using a hypodermic syringe, introduce through the rubber stopper 2 to 10 ml of sterile and pyrogen-free sodium pertechnetate (^{99m}Tc) injection, radioactivity varying as a function of the volume from 0.74 to maximum 11.1 GBq.

Do not use a breather needle as the contents are under nitrogen: after introduction of the volume of sodium pertechnetate (^{99m}Tc) injection, without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial.

Shake for about 2 minutes and allow to rest for 15 minutes at room temperature.

The solution of technetium (^{99mTc})-oxidronate obtained is a clear and colourless solution, with a pH ranging between 5.0 and 7.0.

Limpidity of the solution after preparation, pH, radioactivity and gamma spectrum should be checked before use.

The vial should never be opened and must be kept inside its lead shielding. The solution should be removed aseptically through the stopper with a sterile lead protected syringe.

Quality control

The quality of labelling (radiochemical purity) could be checked according to the following procedure.

Radiochemical purity

Method

Paper chromatography/iTLC-SG chromatography.

The radiochemical purity (RCP) is the percentage of the complexed oxidronate-technetium (^{99m}Tc).

The RCP is determined by the mean of two radiochromatographies: test A and test B.
Test A allows the determination of the hydrolyzed technetium (^{99m}Tc) form (impurity A), test B allows the determination of the free technetium (^{99m}Tc) form (impurity B).
The RCP is then determined by the difference between the whole technetium (^{99m}Tc) content (100%) and the hydrolysed and free technetium (^{99m}Tc) forms (test A and test B).

Operating procedure

Reconstitution
The freeze-dried product is reconstituted by addition of 2 mL of sodium pertechnetate (^{99m}Tc) solution (i.e. 740 – 1110 MBq) through the stopper of the vial.

Procedure
After reconstitution, two chromatographies of the test solution are performed using
Whatman 1 chromatography paper strip for the determination of impurity A and silica gel (iTLC-SG) strip for the determination of impurity B. The mobile phases used for the two migrations are:
- Solvent for test A: 0.9 % sodium chloride solution
- Solvent for test B: methylethylketone

Allow to migrate at room temperature up to the solvent front (about 10 cm for impurity B and 15 cm for impurity A).
The radioactivity distribution is determined with a linear radiochromatogram analyser. Each radioactive spot is identified by calculating of the Rf value.

<u>Plate A:</u>
Region 1A (hydrolysed ^{99m}Tc): from the starting line to the starting line + 2.0 cm [Rf ~ 0.1].
Region 2A (complexed ^{99m}Tc and free ^{99m}Tc): from end of region 1A to the solvent front line + 2.0 cm.

<u>Plate B:</u>
Region 1B (complexed ^{99m}Tc and hydrolysed ^{99m}Tc): from starting line to starting line +4.0 cm [Rf ~ 0 to 0.4].
Region 2B (free ^{99m}Tc): from end of region 1B to solvent front line + 2.0 cm.
Calcultation
The activity of each spot is measured by peak integration. This ratio is expressed as a percentage.
Correct the counting data for background noise.
The percentage of hydrolysed technetium (^{99m}Tc) is calculated from counting data as follows:

The percentage of hydrolysed technetium (^{99m}Tc) is calculated from counting data as follows:

$$\% \text{ hydrolysed } ^{99m}\text{Tc} = \frac{\text{activity of strip A for Region 1A}}{\text{total activity of strip A}} \times 100$$

The percentage of free technetium (^{99m}Tc) is calculated from counting data as follows:

$$\% \text{ free } ^{99m}\text{Tc} = \frac{\text{activity of strip B for Region 2B}}{\text{total activity of strip B}} \times 100$$

The percentage of bound technetium (^{99m}Tc) (radiochemical purity) is calculated according to the following formula:

$$\% \text{ bound } ^{99m}\text{Tc} = 100\% - (\% \text{ hydrolysed } ^{99m}\text{Tc} + \% \text{ free } ^{99m}\text{Tc})$$

Specifications

The content of bound technetium (^{99m}Tc) is not less than 95 %.
The content of free and hydrolysed technetium (^{99m}Tc) does not exceed 5 %.

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