SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

OSTEOCIS 3 mg kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The radionuclide is not part of the kit.

Excipients with known effect
Each vial contains 6.3 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

Posology

Adults and elderly population
The recommended activity for a patient of 70 kg average body weight is 500 MBq (i.e. 300-700 MBq in a 50 to 70 kg adult). Other activities may be justifiable. There is no special dosage regimen for the elderly patient.

Patients with high bone uptake and/or severe renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

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 European Association of Nuclear Medicine (EANM-May 2008) guidelines, by using the formula corresponding to the indication concerned and the relevant correction factor corresponding to the body mass of the young patient (see Table 1).
Recommended activity [MBq] = 35 MBq x Factor (Table 1)

Table 1

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

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. The patient should void before scanning.

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 labelled 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 ratio
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.

In patients with high bone uptake and/or severe 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 (see section 11).
In infants and children particular attention should be paid to the relatively higher radiation exposure of the epiphyses in growing bone.

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as possible during the first hours after the examination 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.

Specific warnings
This medicinal product contains 6.3 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 interaction

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 ^{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 are any) should be offered to the patient.

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

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

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

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 is 4.0 mSv when the maximal recommended activity of 700 MBq is administered these adverse reactions 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 the Yellow Card Scheme, Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.
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4.9 Overdose

In the event of 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: Diagnostic Radiopharmaceuticals, ATC code: V09BA01.

Pharmacodynamic effects
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

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, store at 2 °C – 8 °C (in a refrigerator) 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 reconstitution 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 <and special equipment for use, administration or implantation>

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

Pack size: 5 multidose vials.

6.6 Special precautions for disposal <and other handling>

General warnings
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.

Content of the vial is intended only for use in the preparation of technetium (^{99m}Tc) oxidronate and is not to be administered directly to the patient 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 minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporary 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

CIS bio international
R.N. 306 Saclay
B.P. 32
91192 Gif-sur-Yvette Cedex
FRANCE

8. MARKETING AUTHORISATION NUMBER(S)

PL 11876/0006

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 October 1996
Date of latest renewal: 31 May 2006

10. DATE OF REVISION OF THE TEXT

September 2022

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13×10^5 years can be regarded as quasi stable.
The data listed below are from ICRP publications 53 and 80 for phosphonates and are calculated according to the following assumptions:
The main uptake is in bone, with a further small uptake in kidneys, and the excretion is via the renal system. It is assumed that a fraction of 0.5 of the injected activity is taken up by bone with a half-time of 15 min, and retained there with halftimes of 2 hr (0.3) and 3 d (0.7). In children the uptake is predominantly in the metaphyseal growth zones.
The kidney uptake is set at 0.02 with a retention identical to that of the total body, having half-times (with fractional retention) of 0.5 hr (0.3), 2 hr (0.3) and 3 d (0.4).
In pathological cases there may be higher uptake and/or longer retention in bone, especially in kidney diseases. The 24 hr total body retention, which normally amounts to 30 %, has been reported as 40 % in osteomalacia, 50 % in primary hyperparathyroidism, 60 % in Paget's disease and 90 % in renal osteodystrophia. For absorbed dose calculations in pathological cases an average bone uptake of 70 % is assumed, with no excretion.
Organ absorbed doses and effective doses for normal bone uptake were recalculated in Publication 80.

Radiation exposure (normal bone uptake)
ICRP 80

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	Adult	**Children (age in years)**			
		15	**10**	**5**	**1**
Adrenals	0.0021	0.0027	0.0039	0.0058	0.011
Bladder	0.048	0.060	0.088	0.073	0.13
Bone surfaces	0.063	0.082	0.13	0.22	0.53
Brain	0.0017	0.0021	0.0028	0.0043	0.0061
Breast	0.00071	0.00089	0.0014	0.0022	0.0042
Gall bladder	0.0014	0.0019	0.0035	0.0042	0.0067
GI-tract					
Stomach	0.0012	0.0015	0.0025	0.0035	0.0066
Small intestine	0.0023	0.0029	0.0044	0.0053	0.0095
Colon	0.0027	0.0034	0.0053	0.0061	0.011
Upper large intestine	0.0019	0.0024	0.0039	0.0051	0.0089
Lower large intestine	0.0038	0.0047	0.0072	0.0075	0.013
Heart	0.0012	0.0016	0.0023	0.0034	0.0060
Kidneys	0.0073	0.0088	0.012	0.018	0.032
Liver	0.0012	0.0016	0.0025	0.0036	0.0066
Lungs	0.0013	0.0016	0.0024	0.0036	0.0068
Muscles	0.0019	0.0023	0.0034	0.0044	0.0079
Oesophagus	0.0010	0.0013	0.0019	0.0030	0.0053
Ovaries	0.0036	0.0046	0.0066	0.0070	0.012
Pancreas	0.0016	0.0020	0.0031	0.0045	0.0082
Red marrow	0.0092	0.010	0.017	0.033	0.067
Skin	0.0010	0.0013	0.0020	0.0029	0.0055
Spleen	0.0014	0.0018	0.0028	0.0045	0.0079
Testes	0.0024	0.0033	0.0055	0.0058	0.011
Thymus	0.0010	0.0013	0.0019	0.0030	0.0053
Thyroid	0.0013	0.0016	0.0023	0.0035	0.0056
Uterus	0.0063	0.0076	0.012	0.011	0.018
Remaining organs	0.0019	0.0023	0.0034	0.0045	0.0079
Effective dose (mSv/MBq)	**0.0057**	**0.0070**	**0.011**	**0.014**	**0.027**

The effective dose resulting from the administration of an activity of 700 MBq of technetium (^{99m}Tc)-oxidronate for an adult weighing 70 kg is about 4.0 mSv.
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 33.6 mGy.

Radiation exposure
(high bone uptake and/or severely impaired kidney function)
ICRP 53

Organ	**Absorbed dose per unit activity administered (mGy/MBq)**				
	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**

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.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Usual precautions regarding sterility and radioprotection must be respected.
Withdrawals should be performed under aseptic conditions. The vial must not be opened and must be kept inside the lead shielding. 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.

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

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 15 minutes at room temperature.

The solution of technetium (^{99m}Tc)-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.

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

Method
Paper chromatography / iTLC-SG chromatography

Materials and reagents
1. Adsorbent
   Whatman 1 chromatography paper strip for the determination of impurity A
   Silica gel (iTLC-SG) strip for the determination of impurity B (activated at 110 °C for at least 10 min)
   Trace a starting line 2 cm from one of the ends of each strip.

2. Solvents
   Solvent for impurity A: 0.9 % sodium chloride solution
   Solvent for impurity B: methylethylketone

3. Small developing tanks with cover
   Appropriate tanks. Keep the containers stoppered before use.

4. Miscellaneous
   Forceps, scissors, syringes, needles, appropriate counting apparatus.

Procedure
Do not let air enter the vial to be tested and store all vials containing radioactive solution in lead shieldings.

1. Introduce respectively in tanks A and B a layer of not more than 2 cm of solvents A and B.

2. Apply a drop of the preparation to the starting line of strip A using a syringe and needle. Apply another drop of the preparation to the starting line of strip B.

3. Using forceps, introduce each strip vertically into the corresponding developing tank (i.e. container with solvent A for strip A and container with solvent B for strip B), with the starting line downward. Stopper the containers.

4. Allow to migrate at room temperature up to the solvent front (about 10 cm for impurity B and 15 cm for impurity A) then use the forceps to remove each strip and allow to dry in the air.

5. After identifying the strips, cut strip A at a Rf of mearly 0.1 (corresponding to a distance of nerlay 3.5 - 4 cm from the bottom of the strip) and strip B at Rf = 0.4 (corresponding to a distance of neraly 6 cm from the bottom of the strip).

6. Separately count each section of the strips and record the obtained values (use an appropriate detection apparatus with a constant counting time, and known geometry and background noise).

7. Calculations
   Correct the counting data for background noise.

   Calculate the percentage of hydrolysed technetium (^{99m}Tc) from counting data for the A strip:

   $$\% \text{ hydrolysed } ^{99m}\text{Tc} = \frac{\text{activity of strip A for Rf 0.0- ~0.1}}{\text{total activity of strip A}} \times 100$$

   Calculate the percentage of free technetium (^{99m}Tc) from counting data for the B strip:

   $$\% \text{ free } ^{99m}\text{Tc} = \frac{\text{activity of strip B for Rf 0.4 - 1.0}}{\text{total activity of strip B}} \times 100$$

   Calculate the percentage of bound technetium (^{99m}Tc) (radiochemical purity):
   % bound ^{99m}Tc = 100 % - (% hydrolysed ^{99m}Tc + % free ^{99m}Tc)

8. The percentage of bound ^{99m}Tc (radiochemical purity) should be more than 95 % and the percentage of total hydrolysed ^{99m}Tc and free ^{99m}Tc should be less than 5 %.

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