SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

TECEOS 13 mg kit for radiopharmaceutical preparation.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 13 mg of butedronate tetrasodium (or 3,3-diphosphono-1,2-propanedicarboxylic acid, tetrasodium salt, DPD).

The radionuclide is not part of the kit.

Excipient with known effect:
Each vial contains 3.2 mg of sodium

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
White lyophilised powder.

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)-butedronate obtained is indicated for:

- bone scintigraphy, where it delineates areas of altered osteogenesis.
- cardiac scintigraphy in patients with clinical suspicion of cardiac amyloidosis, in order to detect transthyretin cardiac amyloidosis (ATTR)

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

Bone scintigraphy
The average activity administered by intravenous injection is 500 MBq for an average patient weight of 70 kg and can be adjusted to patient weight (300-700 MBq).

Cardiac scintigraphy
The recommended activity administered by a single intravenous injection is 700 MBq.

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. 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**	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
This medicinal product should be reconstituted before administration to the patient.
For instructions on extemporaneous preparation of the medicinal product before administration, see section 12.

The radiolabelled solution is administered by a single intravenous injection.
For patient preparation, see section 4.4.

Image acquisition
The patient must have emptied his bladder just before image acquisition.

For bone scintigraphy, images are obtained according to the 3-phase bone scan procedure:

- Flow images are obtained shortly after injection to detect abnormal blood flow in skeletal region.
- Blood pool images (tissue phase) should be acquired immediately after the flow portion of the study and completed within 10 minutes of tracer injection.
- Delayed images (skeletal phase) are usually obtained from 2 to 5 hours after injection by whole-body scan.

Additional delayed (6–24-h) images will result in a higher target-to-background ratio and may permit better evaluation of the pelvis if it was obscured by bladder activity on the routine delayed images. It may be particularly helpful in patients with renal insufficiency or urinary retention.

Depending on the indication and the results of planar imaging, additional SPECT acquisitions may be performed to better characterize the presence, location, and extent of disease.

For cardiac imaging, planar whole-body scans are acquired 2 to 3 h after injection and supplemented by planar centered chest images. It is recommended to perform chest SPECT imaging in all cases with positive planar scintigraphy in the cardiac region to:

- avoid overlap of bone uptake;
- distinguish blood-pool activity from myocardial activity;
- assess the regional distribution of myocardial technetium (^{99m}Tc)-butedronate uptake, particularly in the interventricular septum.

4.3. Contraindications

Hypersensitivity to the active substance or to other bisphosphonates, 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 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.

Renal impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible (see section 11). An increased uptake of the tracer may be seen in soft tissues.

In 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.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).
When administering to infants and children, special attention should be paid to the relatively higher radiation dose to the epiphyses in growing bone.

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void just before image acquisition and as often as possible during the first hours after the examination in order to improve the image quality and reduce radiation to the bladder wall.

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

Interpretation of cardiac images
Results should always be interpreted in a broad clinical context. Cardiac uptake of (^{99m}Tc)-butedronate is evaluated using a semi-quantitative visual grading method in relation to bone (rib) uptake at 3 hours (Perugini grade). Visual grades of greater than or equal to 2 on planar or SPECT images are classified as ATTR positive, and grades of less than 2 as ATTR negative.
While grade 2 or 3 is suggestive of ATTR amyloidosis, any degree of (^{99m}Tc)-butedronate myocardial uptake can occasionally be seen in AL amyloidosis. Therefore, (^{99m}Tc)-butedronate scintigraphy should always be interpreted in conjunction with serum and urine immunofixation and serum free light chain assay studies.
Cardiac (^{99m}Tc)-butedronate scintigraphy may be falsely negative for some ATTR gene mutations (Phe64Leu mutation).
Abnormal and diffuse cardiac hyperfixation may be seen in recent extensive myocardial infarction, alcoholic cardiomyopathy, adriamycin-induced cardiotoxicity, pericarditis, pericardial tumours and hypercalcaemia.

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

Specific warnings

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)-butedronate.

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

Teceos contains 3.2 mg of sodium per vial. However, after radiolabeling with sodium pertechnetate (^{99m}Tc), 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 see section 6.6.

4.5. Interactions with other medicinal products and other forms of interaction

As for all other bisphosphonates the following potential interactions have to be taken into account.
Reduced skeletal tracer uptake is observed during treatment with bisphosphonates or denosumab due to competition, and with cabozantinib due to interaction with osteoblast function.

An increased mammary tracer uptake is reported in prostate cancer patients with gynecomastia after androgen deprivation therapy (bicalutamide, oestrogens).

An increased accumulation of the radioactive tracer in tissues other than bone tissue is reported also for:

- medicinal products containing iron,
- acute administration of bisphosphonates,
- several cytostatic and immunosuppressive medicinal products,
- aluminium-containing antacids,
- X-ray contrast media,
- antibiotics,
- antiinflammatory substances,
- injections of calcium gluconate,
- heparin calcium,
- epsilon-aminocaproic acid,
- haematopoietic growth factors,
- nifedipine.

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. 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 doses 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 the foetus. Administration of 700 MBq technetium (^{99m}Tc)-butedronate to a patient results in an absorbed dose to the uterus of 4.3 mGy. Doses above 0.5 mGy are considered a potential risk to the foetus.

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, breast-feeding should be interrupted for 4 hours and the expressed feeds discarded.
Close contact with infants should be restricted during this period.

Fertility

The effect of the administration of technetium-(^{99m}Tc)-butedronate on fertility is unknown.

4.7. Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8. Undesirable effects

Adverse Reactions sorted by MedDRA System Organ Class
Immune system disorders: Hypersensitivity (hot flush, nausea, rash, pruritus)
Frequency: Very rare (<1/10,000)

There are reports in the literature for similar bisphosphonates of the occurrence of skin rashes (4-24 h post injection) and pruritus, of hot flushes during the injection and of nausea. In the case of Teceos such reactions have been observed extremely rarely (about 1 per 1 million applications).

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 3.4 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 the national reporting system:

Statens legemiddelverk
Nettside: www.legemiddelverket.no/meldeskjema

4.9. Overdose

In the event of the administration of a radiation overdose with technetium(^{99m}Tc)-butedronate 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 bladder voiding.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals for skeleton, technetium (^{99m}Tc) compounds.
ATC code: V 09 BA 04.

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

Clinical efficacy and safety
Data from several trials with more than 500 patients in total showed a consistency of diagnostic performance for diagnosis of TTR-type amyloidosis. The positive predictive value of (^{99m}Tc)-butedronate was between 89.7 - 96.0 and the negative predictive value was between 86.2 – 98.6 with different combinations of patients.

5.2. Pharmacokinetic properties

Distribution
In the first few minutes after injection the activity is distributed among abdomen and kidneys. The proceeding clearance from these compartments is demonstrated by an accumulation of activity in the skeletal system. The clearance from blood can be described by a two-phase curve with a half-life of T_1 = 15 min and T_2 = 100 min. In comparison to other bisphosphonates technetium (^{99m}Tc)-butedronate shows the lowest protein binding in plasma. Initially after injection a relatively high level of activity in the plasma is observed which is followed by the rapid clearance from blood. This behaviour could be explained by a reabsorption process in the kidneys.

Organ uptake
Bone scintigraphy is a sensitive but unspecific diagnostic method. The accumulation in the bone depends on the level of blood supply and the extent of the osteogenesis.

Elimination
Compared with other bisphosphonates a smaller amount of activity is excreted in the urine and therefore a high level of technetium(^{99m}Tc)-butedronate is deposited in the skeleton with a maximum 1 hour after injection. Afterwards this level remains constant for several hours. The unchanged complex is eliminated by the kidneys. Around 1 hour after injection 30 % of the administered activity is excreted in the urine. The amount of unlabeled butedronate within the recommended dosage has no influence on the elimination process. The elimination by liver and bowel is negligible.

Half-Life
For healthy persons a whole body retention of 40 ± 4 % of technetium(^{99m}Tc)-butedronate was measured. This value increases in the case of widespread metastases, primary hyperparathyroidism and osteoporosis.

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

5.3. Preclinical safety data

This agent is not intended for regular or continuous administration. Mutagenicity studies and long-term carcinogenicity studies have not been carried out.
Animals suffered no harm from the human dosage in repeated dose toxicity studies in rats and Beagle dogs.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

N-(4-aminobenzoyl)-L-glutamic acid, monosodium salt
tin(II)oxide

6.2. Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 12.
On no account must a solution containing carbohydrate be used for dilution (e.g. glucose, laevulose) and the injection must not be given by means of a slow infusion which contains such solutions. As with other bisphosphonates, in such cases the diagnostic value of the test may be seriously impaired as the bone uptake falls dramatically in favour of massive renal visualization.

6.3. Shelf-life

13 months.
The expiry date is indicated on the outer packaging and on each vial.

After radiolabelling, do not store above 25°C and use within 8 hours.

6.4. Special precautions for storage

Do not store the kit above 25°C.
For storage conditions after radiolabeling of the medicinal product, see section 6.3.

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

6.5. Nature and contents of container

15-ml colourless type I glass vial, closed with a bromobutyl stopper and polypropylene lid, welded to an aluminium crimp capsule.

Pack size: 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)-butedronate injection 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 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) 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 spills 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
RN 306 - Saclay
BP 32
F-91192, GIF-SUR-YVETTE Cedex
France

8. MARKETING AUTHORISATION NUMBER

99-4548

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation : 08/05/2001
Date of latest renewal : 08/05/2011

10. DATE OF REVISION OF THE TEXT

11.06.2025

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 x 105 years can be regarded as quasi stable.

The data listed below are from ICRP publications 128 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.

Radiation exposure (normal bone uptake)

ORGAN	DOSE ABSORBED PER ACTIVITY ADMINISTERED (mGy/MBq)				
	Adults	**15 year old**	**10 year old**	**5 year old**	**1 year old**
Adrenal glands	0.0021	0.0026	0.0038	0.0058	0.011
Bone surfaces	0.034	0.015	0.023	0.038	0.082
Brain	0.0017	0.0020	0.0028	0.0042	0.0059
Breasts	0.00069	0.00086	0.0013	0.0021	0.0040
Gall bladder	0.0014	0.0018	0.0033	0.0043	0.0065
Gastrointestinal tract					
Stomach	0.0012	0.0014	0.0024	0.0036	0.0064
Small intestine	0.0022	0.0028	0.0043	0.0061	0.0093
Colon	0.0027	0.0034	0.0052	0.0072	0.010
Upper large intestine	0.0019	0.0024	0.0038	0.0057	0.0087
Lower large intestine	0.0038	0.0047	0.0071	0.0092	0.013
Heart	0.0012	0.0015	0.0022	0.0033	0.0059
Kidneys	0.0072	0.0087	0.012	0.018	0.031
Liver	0.0012	0.0016	0.0024	0.0036	0.0064
Lungs	0.0012	0.0016	0.0023	0.0035	0.0067
Muscles	0.0018	0.0022	0.0033	0.0047	0.0077
Oesophagus	0.0010	0.0013	0.0019	0.0029	0.0051
Ovaries	0.0036	0.0045	0.0065	0.0086	0.012
Pancreas	0.0016	0.0020	0.0030	0.0045	0.0079
Red bone marrow	0.0059	0.0054	0.0088	0.017	0.036
Skin	0.00099	0.0013	0.0019	0.0030	0.0053
Spleen	0.0014	0.0018	0.0027	0.0044	0.0077
Testes	0.0024	0.0033	0.0054	0.0075	0.010
Thymus	0.0010	0.0013	0.0019	0.0029	0.0051
Thyroid	0.0013	0.0015	0.0022	0.0034	0.0054
Urinary bladder wall	0.047	0.059	0.087	0.11	0.13
Uterus	0.0062	0.0075	0.011	0.014	0.018
Remaining organs	0.0019	0.0023	0.0034	0.005	0.0077
Effective dose (mSv/MBq)	**0.0049**	**0.0057**	**0.0086**	**0.012**	**0.018**

The effective dose resulting from the administration of a (maximal recommended) activity of 700 MBq of technetium (^{99m}Tc)-butedronate, for a healthy adult weighing 70 kg is about 3.4 mSv. For an administered activity of 700 MBq the typical radiation dose to the target organ (bone) is 23.8 mGy and the typical radiation dose to the critical organ (bladder wall) is 32.9 mGy.

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 preparation

Procedure for the preparation of technetium (^{99m}Tc)-butedronate

TECEOS is a kit for the preparation of technetium (^{99m}Tc)-butedronate Injection, containing a sterile, progen-free, freeze-dried product under vacuum.

The product 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)-butedronate injection.

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 370 to maximum 11100 MBq. Sodium pertechnetate (^{99m}Tc) injection should comply with European Pharmacopoeia specifications.

Do not use a breather needle as the content is under vacuum.

Shake for about 5 minutes.

The solution of technetium (^{99m}Tc)-butedronate obtained is a clear and colorless solution, free from visible particles with a pH ranging between 6.5 and 7.5.

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

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 radiochemical purity of the final radiolabelled preparation can be tested according to one of the following procedures:

Methods
Thin Layer Chromatography (TLC) or ascending paper chromatography

Thin Layer Chromatography

Materials and reagents

1. Chromatography support: two fiberglass plates A and B coated with silica gel (ITLC-SG, 2.5 × 20 cm), previously heated at 110 ° C for 10 min and cooled to room temperature before use. Trace a thin line called “deposit line” 2 cm from the bottom of each support. Draw a thin line called "solvent frontline” 15 cm from the “deposit line”.

2. Mobile phases:
   A:1M sodium acetate solution
   B: Methyl ethyl ketone

3. Chromatography tanks
   Two glass tanks A and B of appropriate size fitted with a lid ensuring a tight seal.

4. Miscellaneous
   Forceps, syringes, needles, appropriate counter unit.

Procedure

1. Introduce a sufficient volume of the corresponding mobile phase (approx. 1.5 cm deep) into tanks A and B. Allow to equilibrate for approx. 30 min.

2. By using a syringe equipped with a needle, apply a drop of the solution to be tested (approx. 1 to 5 µl) on the “deposit line” of each plate.
   Proceed quickly to avoid any degradation of the solution. Do not allow the spot to dry.

3. By using forceps, introduce each plate in the tank containing the corresponding mobile phase, then close the lid. Lower the support into the mobile phase by letting the “deposit line” above the surface of solvent. Allow the solvent to migrate up to the "solvent frontline” (approx. 10 min. development time).

4. Remove the plates with forceps and allow to air dry.

5. Determine the distribution of radioactivity by using an appropriate detector.
   Measure the radioactivity of each spot by peak integration.
   With mobile phase A, Rf of hydrolysed (^{99m}Tc) is 0, whereas Rf of (free (^{99m}Tc) + ^{99m}Tc-butedronate) is around 0.8 - 1.0.
   With mobile phase B, Rf of free (^{99m}Tc) is around 1.0, whereas Rf of (hydrolysed (^{99m}Tc) + ^{99m}Tc-butedronate) is 0.

6. Calculations

   $$\%\ \text{free}\ (^{99m}\text{Tc}) = \frac{\text{Radioactivity of the spot at Rf 1}}{\text{Total radioactivity of the plate B}} \times 100$$

   $$\%\ \text{hydrolysed}\ (^{99m}\text{Tc}) = \frac{\text{Radioactivity of the spot at Rf 0}}{\text{Total radioactivity of the plate A}} \times 100$$

   % (^{99m}Tc)-butedronate = 100 % - [% free (^{99m}Tc) +% hydrolysed (^{99m}Tc)]

7. The percentage of (^{99m}Tc)-butedronate must be equal to at least 95 %, the percentage of free (^{99m}Tc) should not exceed 2.0 % and the percentage of hydrolysed (^{99m}Tc) should not exceed 2.0 %.

Ascending paper chromatography

Materials and reagents

1. Chromatographic systems
   Chromatographic system A:
   Support A: Whatman 31ET type (2.5 × 20 cm)
   Mobile phase A: 1M sodium chloride solution

   Chromatographic system B:
   Support B: Whatman 1 type (2.5 × 20 cm)
   Mobile phase B: methyl ethyl ketone

   Trace a thin line called “deposit line” 2 cm from the bottom of each support. Draw a thin line called “solvent frontline” 10 cm from the “deposit line”.

2. Chromatography tanks
   Two glass tanks A and B of appropriate size fitted with a lid ensuring a tight seal.

3. Miscellaneous
   Forceps, syringes, needles, appropriate counter unit

Procedure

1. Introduce a sufficient volume of the corresponding mobile phase (approx. 1.5 cm deep) into tanks A and B. Allow to equilibrate for approx. 30 min.

2. By using a syringe equipped with a needle, apply a drop of the solution to be tested (approx. 1 to 5 µl) on the “deposit line” of each support.
   Proceed quickly to avoid any degradation of the solution. Do not allow the spot to dry.

3. By using forceps, introduce each support in the tank containing the corresponding mobile phase, and then close the lid. Lower the support into the mobile phase by letting the “deposit line” above the surface of solvent. Allow the solvent to migrate up to the “solvent frontline” (approx. 20 min. development time).

4. Remove the supports with forceps and allow to air dry.

5. Determine the distribution of radioactivity by using an appropriate detector.
   Measure the radioactivity of each spot by peak integration.
   With the chromatographic system B, Rf of free (^{99m}Tc) is around 1.0, whereas Rf of (hydrolysed (^{99m}Tc) + ^{99m}Tc-butedronate) is 0 and with the chromatographic system A, Rf of hydrolysed (^{99m}Tc) is 0, whereas Rf of (free (^{99m}Tc) + ^{99m}Tc-butedronate) is around 0.7 - 1.0.

6. Calculations

$$\% \text{ free } (^{99m}\text{Tc}) = \frac{\text{Radioactivity of the spot at Rf 1}}{\text{Total radioactivity of the support B}} \times 100$$

$$\% \text{ hydrolysed } (^{99m}\text{Tc}) = \frac{\text{Radioactivity of the spot at Rf 0}}{\text{Total radioactivity of the support A}} \times 100$$

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

7. The percentage of technetium (^{99m}Tc)-butedronate must be equal to at least 95 %, the percentage of free (^{99m}Tc) should not exceed 2.0 % and the percentage of hydrolysed (^{99m}Tc) should not exceed 2.0 %.

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

Detaljert informasjon om dette legemidlet er tilgjengelig på nettstedet til Statens Legemiddelverk NOMA (www.legemiddelverket.no).