SUMMARY OF PRODUCT CHARACTERISTICS
for
TECEOS, kit for radiopharmaceutical preparation

1. NAME OF THE MEDICINAL PRODUCT
TECEOS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Each 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.

4.2. Posology and method of administration

Posology
Adults and elderly population
The average activity administered is 500 MBq (300-700 MBq) on a patient of average weight (70 kg). Other activities may be justifiable.

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 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 \[\text{[MBq]} = 35 \text{ MBq} \times \text{Factor (Table 1)}\]

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

*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.

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.
4.3. **Contraindications**
Hypersensitivity to the active substance or to other 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 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).

**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 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.

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

**Specific warnings**
Inadvertent or accidental subcutaneous administration of technetium($^{99m}$Tc)-butedronate should be avoided as perivascular inflammation has been described for technetium($^{99m}$Tc)diphosphonates.
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 diphosphonates the following potential interactions have to be taken into account.

An increased extraosseous accumulation of the radiotracer is reported for:

- iron containing drugs,
- acute administration of diphosphonates,
- several cytostatic and immunosuppressive drugs,
- aluminium-containing antacids,
- X-ray contrast media,
- antibiotics,
- anti-inflammatory substances,
- injections of calcium gluconate,
- heparin calcium and
- ε-amino caproic acid.

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 (99mTc)-butedronate to a patient with normal bone uptake results in an absorbed dose to the uterus of 4.41 mGy.

**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-(99mTc)-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: very rare (<1/10,000)

Gastro-intestinal disorders: nausea: very rare (<1/10,000)

Skin and subcutaneous disorders: rash, pruritus: very rare (<1/10,000)

General disorders and administration site conditions: hot flush: (very rare) (<1/10,000)

There are reports in the literature for similar diphosphonates 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 4.0 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:

<table>
<thead>
<tr>
<th>Denmark</th>
<th>Finland</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lægemiddelstyrelsen</td>
<td>www-sivusto: <a href="http://www.fimea.fi">www.fimea.fi</a></td>
</tr>
<tr>
<td>Axel Heides Gade 1</td>
<td>Lääkealan turvallisuus- ja</td>
</tr>
<tr>
<td>DK-2300 København S</td>
<td>kehittämikeskus Fimea</td>
</tr>
<tr>
<td>Websted: <a href="http://www.meldenbivirkning.dk">www.meldenbivirkning.dk</a></td>
<td>Lääkkeiden haittavaikutusrekisteri</td>
</tr>
<tr>
<td>E-mail: <a href="mailto:dkma@dkma.dk">dkma@dkma.dk</a></td>
<td>PL 55</td>
</tr>
<tr>
<td></td>
<td>FI-00034 Fimea</td>
</tr>
</tbody>
</table>

4.9. Overdose

In the event of the administration of a radiation overdose with technetium (99mTc)-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 (99mTc) compounds.

ATC code: V 09 BA 04

At the chemical concentrations used for diagnostic examinations technetium (99mTc)-butedronate does not appear to have any pharmacodynamic activity.
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 diphosphonates 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 diphosphonates 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 whole body retention of $40 \pm 4$ % 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-aminobenzyl)-L-glutamic acid, monosodium salt
Stannous oxide
Sodium hydroxide (for pH adjustment)
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 diphosphonates, in such cases the diagnostic value of the test may be seriously impaired as the bone uptake falls dramatically in favour of massive renal visualisation.

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 radiolabelling 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, 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 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 ($^{99m}\text{Tc}$) 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 medicinal 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

Denmark: DK R 1171
Finland: 11229

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: Date of latest renewal:
Finland: 29/11/1993 18/08/2009

10. DATE OF REVISION OF THE TEXT

Denmark: 2 June 2016
Finland: 4.11.2016

11. DOSIMETRY

Technetium ($^{99m}\text{Tc}$) is produced by means of a ($^{99}\text{Mo}/^{99m}\text{Tc}$) 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 ($^{99}\text{Tc}$) which, in view of its long half-life of $2.13 \times 10^{5}$ 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 half-times 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).

**Radiation exposure (normal bone uptake)**- from ICRP publication 80.

<table>
<thead>
<tr>
<th>ORGAN</th>
<th>ABSORBED DOSE PER UNIT ACTIVITY ADMINISTERED (mGy/MBq)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adult</td>
</tr>
<tr>
<td>Adrenals</td>
<td>0.0021</td>
</tr>
<tr>
<td>Bladder</td>
<td>0.048</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>0.063</td>
</tr>
<tr>
<td>Brain</td>
<td>0.0017</td>
</tr>
<tr>
<td>Breast</td>
<td>0.00071</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>0.0014</td>
</tr>
<tr>
<td>GI-tract</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>0.0012</td>
</tr>
<tr>
<td>Small intest</td>
<td>0.0023</td>
</tr>
<tr>
<td>Colon</td>
<td>0.0027</td>
</tr>
<tr>
<td>ULI wall</td>
<td>0.0019</td>
</tr>
<tr>
<td>LLI wall</td>
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</tr>
<tr>
<td>Heart</td>
<td>0.0012</td>
</tr>
<tr>
<td>Kidneys</td>
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</tr>
<tr>
<td>Liver</td>
<td>0.0012</td>
</tr>
<tr>
<td>Lungs</td>
<td>0.0013</td>
</tr>
<tr>
<td>Muscles</td>
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</tr>
<tr>
<td>Oesophagus</td>
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</tr>
<tr>
<td>Ovaries</td>
<td>0.0036</td>
</tr>
<tr>
<td>Pancreas</td>
<td>0.0016</td>
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<tr>
<td>Red marrow</td>
<td>0.0092</td>
</tr>
<tr>
<td>Skin</td>
<td>0.0010</td>
</tr>
<tr>
<td>Spleen</td>
<td>0.0014</td>
</tr>
<tr>
<td>Testes</td>
<td>0.0024</td>
</tr>
<tr>
<td>Thymus</td>
<td>0.0010</td>
</tr>
<tr>
<td>Thyroid</td>
<td>0.0013</td>
</tr>
<tr>
<td>Uterus</td>
<td>0.0063</td>
</tr>
<tr>
<td>Remaining organs</td>
<td>0.0019</td>
</tr>
<tr>
<td><strong>Effective dose (mSv/MBq)</strong></td>
<td><strong>0.0057</strong></td>
</tr>
</tbody>
</table>

The effective dose resulting from the administration of a (maximal recommended) activity of 700 MBq of technetium(99mTc)-butedronate, for a healthy 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.
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 (99mTc)-butedronate

TECEOS is a kit for the preparation of technetium (99mTc)-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 (99mTc) injection, allowing the preparation of technetium (99mTc)-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 (99mTc) injection, radioactivity varying as a function of the volume from 370 to maximum 11100 MBq. Sodium pertechnetate (99mTc) 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 (99mTc)-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 (99mTc) is 0, whereas Rf of (free (99mTc) + 99mTc-butedronate) is around 0.8 - 1.0.
   With mobile phase B, Rf of free (99mTc) is around 1.0, whereas Rf of (hydrolysed (99mTc) + 99mTc-butedronate) is 0.
6. Calculations

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

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

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

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

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

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

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

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.

Denmark: Detailed information on this medicinal product is available on the website of Lægemiddelstyrelsens hjemmeside http://www.dkma.dk.

Finland: Detailed information on this medicinal product is available on the website www.laakelaitos.fi