NANOCIS

Kit for the preparation of technetium $[^{99m}\text{Tc}]$ colloidal rhenium sulphide injection (Nanocolloid)

SUMMARY OF PRODUCT CHARACTERISTICS
1. **NAME OF THE MEDICINAL PRODUCT**

NANOCIS
Kit for the preparation of technetium $[^{99m}\text{Tc}]$ colloidal rhenium sulphide injection (Nanocolloid)

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

The kit contains all the non radioactive reagents (vials A and vials B) required for five preparations of colloidal rhenium sulphide injection (Nanocolloid), labeled with technetium $[^{99m}\text{Tc}]$.

Each vial A contains under nitrogen 1 mL of sterile, pyrogen-free solution and the following active substance

Rhenium sulphide : 0.15 mg of elemental rhenium, i.e. 0.24 mg of Re$_2$S$_7$

For excipients, see 6.1.

The product contains no antimicrobial preservative.

3. **PHARMACEUTICAL FORM**

Kit for radiopharmaceutical preparation.
Powder and solvent for solution for injection.

4. **CLINICAL PARTICULARS**

4.1. **Therapeutic indications**

This medicinal product is for diagnostic use only.

After labeling with sodium pertechnetate $[^{99m}\text{Tc}]$ solution for injection :

- Lymphography
- Digestive exploration (gastroesophageal scintigraphy).
4.2. Posology and method of administration

**Lymphography**

The dosage of technetium \[^{99m}\text{Tc}\] colloidal rhenium sulphide injection to an adult is 18.5-185 MBq given by single or multiple subcutaneous (interstitial) injection(s), other doses may be justifiable. The amount of radiopharmaceutical is usually below 20 MBq per injection site, depending on the anatomical areas to be investigated and the time interval between injection and imaging. A maximum volume of 0.5 mL per injection site should not be exceeded. Recommended volumes are 0.2-0.3 mL.

The injection site is to be selected according to the anatomical area under investigation and is made without pressure into loose connective tissue which should not be poorly vascularized. Prior to injection, an aspiration test should ascertain that no blood vessel was inadvertently punctured.

The dose per injection site can be reduced in children, but a minimum dose of about 5-10 MBq per injection site is necessary to obtain images of sufficient quality.

**Study of the Gastro Oesophageal Reflux**

For adults, the patient receives an oral dosage of 3.7 to 11.1 MBq of technetium \[^{99m}\text{Tc}\] colloidal rhenium sulphide (other doses may be justifiable) in a liquid phase in accordance with local practice. Dynamic scintigraphy may be performed along with static imaging.

For children 3.7 to 11.1 MBq is given in a liquid phase according to local practice.

4.3. Contraindications

None known.

4.4. Special warnings and special precautions for use

Lymphoscintigraphy is not advised in patients with complete block of the lymphatic system (e.g. after contrast lymphangiography), particularly in the lower extremities, because of the potential radiation hazard at the injection sites.

In some cases, administration of the product can involve allergic side effects. Adequate medication and reanimation equipment must therefore always be kept available during the investigation.

This radiopharmaceutical may only be used and administered by authorised persons.

Radiopharmaceuticals intended for administration to patients should be prepared by the user in a manner which satisfies both radiological safety and pharmaceutical quality requirements.
4.5. Interactions with other medicinal products and other forms of interaction

The use of local anaesthetic agents or hyaluronidase prior to administering the labelled preparation have shown to disturb lymphatic uptake.

4.6. Pregnancy and lactation

When it is necessary to administer radioactive medicinal products to a woman of childbearing potential, information should always be sought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainty exists, it is important that the radiation exposure should be the minimum consistent with achieving the desired clinical information. Alternative techniques which do not involve ionising radiation should be considered.

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

Before administering a radioactive medicinal product to a mother who is breast feeding, consideration should be given as to whether the investigation could be reasonably delayed until the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceutical has been made, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, the breast feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the level in milk will not result in a radiation dose to the child greater than 1 mSv.

4.7. Effects on ability to drive and use machines

Not relevant

4.8. Undesirable effects

In some cases, administration of the product can involve allergic side effects. Adequate medication and reanimation equipment must therefore always be kept available during the investigation.

The injection of the hypertonic technetium [$^{99m}$Tc] rhenium sulphide colloidal solution can produce pain at the injection site.

For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefit. The activity administered must be such that the resulting radiation dose is as low as reasonably achievable bearing in mind the need to obtain the intended diagnostic or therapeutic result.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse effects will occur with low frequency because of the low radiation dose incurred.
For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered \( (E) \) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9. Overdose

In the event of the administration of a radiation overdose, the absorbed dose to the patient undergoing gastroesophageal scintigraphy can be reduced by increasing the elimination of the radionuclide from the body.

In the event of the administration of a radiation overdose, the absorbed dose to the patient undergoing lymphography can not be reduced due to poor elimination of the radionuclide from the body.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Radiopharmaceutical preparation for diagnostic use.
ATC code: V09DB06

At doses used for diagnostic procedures, technetium \(^{99m}\text{Tc}\) colloidal rhenium sulphide doses not appear to exert any pharmacodynamic effects.

5.2. Pharmacokinetic properties

* Subcutaneous injection:
  Technetium \(^{99m}\text{Tc}\) colloidal rhenium sulphide is administered by subcutaneous injection, generally at the level of the interdigital spaces of the hands or feet.

The lymphatic capillaries have a discontinuous wall without a basal membrane, endowed with pores which allow very ready passage of the interstitial liquid into the lymph ducts. The liquid is deposited in the interstitial space of the region to be investigated, allowing particles of size similar to albumin to cross the lymphatic capillary pores and migrate into the lymph where they are phagocytosed in the lymph nodes by the bordering cells of the reticuloendothelial system. The phenomenon is repeated from one lymph node to the next.

The product is a metallic colloid which is therefore taken up by the first lymph node group, but the presence of gelatine protects the colloid and allows it to traverse this first group.

The lymph node level shows binding of \(3.06 \pm 0.10\%\) of the administered activity at the first hour, and \(3.83 \pm 0.16\%\) at the third hour.

Passage into the vascular sector is negligible, in the first hour following administration.

Experimental data show urinary and hepatic elimination of the injected product. 11 % of the injected activity is recovered in the hepatic parenchyma after 3 hours. Vesical binding gradually increases, to reach 14.6 % of the injected activity at the 60\textsuperscript{th} minute.
Technetium $[^{99m}\text{Tc}]$ colloidal rhenium sulphide administered per os is not absorbed from the gastro-intestinal tract.

5.3. Preclinical safety data

The mean lethal i.p. dose for potassium perrhenate is about 2.8 g/kg in mice. Expressed with reference to rhenium, the LD$_{50}$ is 180 mg/kg.

Acute intravenous toxicity in mice of rhenium sulphide nanocolloid gives no abnormal reaction after injection of the preparation containing 2.5 mg rhenium sulphide/kg and 50 mg sodium pyrophosphate/kg and for the 7 subsequent days.

In rat, the LD$_{50}$ (5 minutes) after i.v. injection of stannous pyrophosphate is 41.0 ± 1.6 mg/kg.

For a subcutaneous injection of 185 MBq in man, the quantity of sodium pyrophosphate is 0.007 mg/kg, i.e. 12,500 times less than the LD$_{50}$ by the intravenous route in the mouse, and the quantity of stannous chloride is 0.001 mg/kg, i.e. 23,000 times less than the LD$_{50}$ in the mouse.

Sodium pyrophosphate in the presence of stannous chloride: Acute intravenous toxicity in the mouse gives a LD$_{50}$ of 100 mg Na$_4$P$_2$O$_7$, 10 H$_2$O/kg.

Mutagenicity, teratogenicity or long-term carcinogenicity studies have not been carried out.

5.4. Dosimetry

The radiation doses absorbed by a patient (70 kg individual) after subcutaneous administration of technetium $[^{99m}\text{Tc}]$ colloidal rhenium sulphide are calculated from the model published by Bergqvist et al. (1982, J Nucl Med 23). The model has been applied using the pharmacokinetic data presented in section 5.2.

The maximum dose at the injection site for an activity of 37 MBq distributed in a tissue volume of 10 mL is 0.35 Gy.

The following doses have been calculated for an activity injected s.c. near the umbilicus.

<table>
<thead>
<tr>
<th>Organ</th>
<th>Radiation dose $\mu$Gy / MBq</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymph node</td>
<td>&lt; 80</td>
</tr>
<tr>
<td>Gonads</td>
<td></td>
</tr>
<tr>
<td>Ovaries</td>
<td>2.4</td>
</tr>
<tr>
<td>Testes</td>
<td>0.62</td>
</tr>
<tr>
<td>Liver</td>
<td>17.4</td>
</tr>
<tr>
<td>Spleen</td>
<td>20.2</td>
</tr>
<tr>
<td>Kidney</td>
<td>12.4</td>
</tr>
<tr>
<td>Bladder</td>
<td>16.9</td>
</tr>
<tr>
<td>Other organs</td>
<td>4</td>
</tr>
</tbody>
</table>
For this product, the effective dose equivalent to the lymph nodes resulting from an administered activity of 185 MBq is typically 2 mSv (per 70 kg individual).

Technetium $^{99m}$Tc disintegrates with the emission of gamma radiation with the energy of 140 keV and a half life of 6 hours to technetium $^{99}$Tc which can be regarded as quasi stable.

* Dosimetry data on p.o. administration:

The doses of radiation absorbed from technetium $^{99m}$Tc colloidal rhenium sulphide are laid down by the International Commission of Radiological Protection, ICRP Publication 80 (Radiation dose to patients from radiopharmaceuticals).

**Tc-LABELLED NON-ABSORBABLE MARKERS**

**Oral administration of fluids**

<table>
<thead>
<tr>
<th>Organ</th>
<th>Adult</th>
<th>15 years</th>
<th>10 years</th>
<th>5 years</th>
<th>1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adrenals</td>
<td>$2.5 \times 10^{-3}$</td>
<td>$3.3 \times 10^{-3}$</td>
<td>$5.5 \times 10^{-3}$</td>
<td>$8.9 \times 10^{-3}$</td>
<td>$1.5 \times 10^{-2}$</td>
</tr>
<tr>
<td>* Bladder wall</td>
<td>$6.9 \times 10^{-3}$</td>
<td>$9.1 \times 10^{-3}$</td>
<td>$1.4 \times 10^{-2}$</td>
<td>$2.2 \times 10^{-2}$</td>
<td>$3.5 \times 10^{-2}$</td>
</tr>
<tr>
<td>Bone surfaces</td>
<td>$4.2 \times 10^{-3}$</td>
<td>$5.2 \times 10^{-3}$</td>
<td>$7.4 \times 10^{-3}$</td>
<td>$1.1 \times 10^{-3}$</td>
<td>$2.1 \times 10^{-2}$</td>
</tr>
<tr>
<td>Brain</td>
<td>$1.8 \times 10^{-6}$</td>
<td>$3.4 \times 10^{-6}$</td>
<td>$1.2 \times 10^{-5}$</td>
<td>$4.0 \times 10^{-5}$</td>
<td>$1.0 \times 10^{-4}$</td>
</tr>
<tr>
<td>Breast</td>
<td>$2.8 \times 10^{-4}$</td>
<td>$4.2 \times 10^{-4}$</td>
<td>$9.4 \times 10^{-4}$</td>
<td>$2.0 \times 10^{-3}$</td>
<td>$3.8 \times 10^{-3}$</td>
</tr>
<tr>
<td>Gall bladder</td>
<td>$1.4 \times 10^{-2}$</td>
<td>$1.8 \times 10^{-2}$</td>
<td>$3.0 \times 10^{-2}$</td>
<td>$4.3 \times 10^{-2}$</td>
<td>$7.1 \times 10^{-2}$</td>
</tr>
<tr>
<td>GI-tract</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>* Stomach</td>
<td>$2.2 \times 10^{-2}$</td>
<td>$2.9 \times 10^{-2}$</td>
<td>$4.1 \times 10^{-2}$</td>
<td>$6.6 \times 10^{-2}$</td>
<td>$1.2 \times 10^{-1}$</td>
</tr>
<tr>
<td>* SI</td>
<td>$6.0 \times 10^{-2}$</td>
<td>$7.6 \times 10^{-2}$</td>
<td>$1.2 \times 10^{-1}$</td>
<td>$1.9 \times 10^{-1}$</td>
<td>$3.5 \times 10^{-1}$</td>
</tr>
<tr>
<td>* Colon</td>
<td>$1.0 \times 10^{-1}$</td>
<td>$1.3 \times 10^{-1}$</td>
<td>$2.2 \times 10^{-1}$</td>
<td>$3.5 \times 10^{-1}$</td>
<td>$6.6 \times 10^{-1}$</td>
</tr>
<tr>
<td>* (ULI)</td>
<td>$1.2 \times 10^{-1}$</td>
<td>$1.5 \times 10^{-1}$</td>
<td>$2.5 \times 10^{-1}$</td>
<td>$4.0 \times 10^{-1}$</td>
<td>$7.5 \times 10^{-1}$</td>
</tr>
<tr>
<td>* (LLI)</td>
<td>$8.3 \times 10^{-2}$</td>
<td>$1.1 \times 10^{-1}$</td>
<td>$1.8 \times 10^{-1}$</td>
<td>$2.9 \times 10^{-1}$</td>
<td>$5.4 \times 10^{-1}$</td>
</tr>
<tr>
<td>Heart</td>
<td>$1.0 \times 10^{-3}$</td>
<td>$1.4 \times 10^{-3}$</td>
<td>$2.5 \times 10^{-3}$</td>
<td>$4.3 \times 10^{-3}$</td>
<td>$8.6 \times 10^{-3}$</td>
</tr>
<tr>
<td>Kidneys</td>
<td>$5.5 \times 10^{-3}$</td>
<td>$6.7 \times 10^{-3}$</td>
<td>$1.0 \times 10^{-2}$</td>
<td>$1.5 \times 10^{-2}$</td>
<td>$2.3 \times 10^{-2}$</td>
</tr>
<tr>
<td>Liver</td>
<td>$3.7 \times 10^{-3}$</td>
<td>$4.8 \times 10^{-3}$</td>
<td>$9.3 \times 10^{-3}$</td>
<td>$1.5 \times 10^{-2}$</td>
<td>$2.7 \times 10^{-2}$</td>
</tr>
<tr>
<td>Lungs</td>
<td>$5.7 \times 10^{-4}$</td>
<td>$9.1 \times 10^{-4}$</td>
<td>$1.6 \times 10^{-3}$</td>
<td>$2.9 \times 10^{-3}$</td>
<td>$5.7 \times 10^{-3}$</td>
</tr>
<tr>
<td>Muscles</td>
<td>$3.2 \times 10^{-3}$</td>
<td>$4.0 \times 10^{-3}$</td>
<td>$6.0 \times 10^{-3}$</td>
<td>$9.0 \times 10^{-3}$</td>
<td>$1.5 \times 10^{-2}$</td>
</tr>
<tr>
<td>Oesophagus</td>
<td>$1.9 \times 10^{-4}$</td>
<td>$3.0 \times 10^{-4}$</td>
<td>$5.0 \times 10^{-4}$</td>
<td>$1.2 \times 10^{-3}$</td>
<td>$2.6 \times 10^{-3}$</td>
</tr>
<tr>
<td>Ovaries</td>
<td>$2.5 \times 10^{-2}$</td>
<td>$3.2 \times 10^{-2}$</td>
<td>$4.8 \times 10^{-2}$</td>
<td>$6.8 \times 10^{-2}$</td>
<td>$1.1 \times 10^{-1}$</td>
</tr>
<tr>
<td>Pancreas</td>
<td>$5.9 \times 10^{-3}$</td>
<td>$7.9 \times 10^{-3}$</td>
<td>$1.2 \times 10^{-2}$</td>
<td>$1.8 \times 10^{-2}$</td>
<td>$3.1 \times 10^{-2}$</td>
</tr>
<tr>
<td>Red marrow</td>
<td>$4.7 \times 10^{-3}$</td>
<td>$5.7 \times 10^{-3}$</td>
<td>$7.5 \times 10^{-2}$</td>
<td>$9.2 \times 10^{-2}$</td>
<td>$1.1 \times 10^{-1}$</td>
</tr>
<tr>
<td>Skin</td>
<td>$9.3 \times 10^{-4}$</td>
<td>$1.1 \times 10^{-3}$</td>
<td>$1.7 \times 10^{-3}$</td>
<td>$2.9 \times 10^{-3}$</td>
<td>$5.4 \times 10^{-3}$</td>
</tr>
<tr>
<td>Spleen</td>
<td>$4.0 \times 10^{-3}$</td>
<td>$5.0 \times 10^{-3}$</td>
<td>$7.8 \times 10^{-3}$</td>
<td>$1.2 \times 10^{-2}$</td>
<td>$2.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>Testes</td>
<td>$1.3 \times 10^{-3}$</td>
<td>$2.0 \times 10^{-3}$</td>
<td>$3.8 \times 10^{-3}$</td>
<td>$6.5 \times 10^{-3}$</td>
<td>$1.2 \times 10^{-2}$</td>
</tr>
<tr>
<td>Thymus</td>
<td>$1.9 \times 10^{-4}$</td>
<td>$3.0 \times 10^{-4}$</td>
<td>$5.0 \times 10^{-4}$</td>
<td>$1.2 \times 10^{-3}$</td>
<td>$2.6 \times 10^{-3}$</td>
</tr>
<tr>
<td>Thyroid</td>
<td>$2.0 \times 10^{-5}$</td>
<td>$4.8 \times 10^{-5}$</td>
<td>$1.5 \times 10^{-4}$</td>
<td>$3.0 \times 10^{-4}$</td>
<td>$1.2 \times 10^{-3}$</td>
</tr>
<tr>
<td>Uterus</td>
<td>$1.6 \times 10^{-2}$</td>
<td>$2.0 \times 10^{-2}$</td>
<td>$3.1 \times 10^{-2}$</td>
<td>$4.7 \times 10^{-2}$</td>
<td>$7.6 \times 10^{-2}$</td>
</tr>
<tr>
<td>Remaining organs</td>
<td>$5.2 \times 10^{-3}$</td>
<td>$7.2 \times 10^{-3}$</td>
<td>$1.1 \times 10^{-2}$</td>
<td>$2.0 \times 10^{-2}$</td>
<td>$3.0 \times 10^{-2}$</td>
</tr>
<tr>
<td>Effective dose</td>
<td>$1.9 \times 10^{-2}$</td>
<td>$2.5 \times 10^{-2}$</td>
<td>$3.9 \times 10^{-2}$</td>
<td>$6.2 \times 10^{-2}$</td>
<td>$1.1 \times 10^{-1}$</td>
</tr>
</tbody>
</table>

For this product the effective dose equivalent resulting from a p.o. administered activity of 11.1 MBq is typically 0.21 mSv (per 70 kg individual).
6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of excipients**

Vial A (under nitrogen atmosphere):

Gelatin  
Ascorbic acid  
Sodium hydroxide  
Concentrated hydrochloric acid  
Water for injections

Vial B (under nitrogen atmosphere):

Sodium pyrophosphate decahydrate  
Stannous chloride dihydrate  
Sodium hydroxide

6.2. **Incompatibilities**

None known.

6.3. **Shelf-life**

The expiry date for the kit is 6 months from the date of manufacture. The expiry date is indicated on the outer packaging and on each vial. The labeled product should be used within 4 hours after labelling.

6.4. **Special precautions for storage**

Store the kit at 2°C - 8°C (in a refrigerator). Do not store the labeled product above 25°C. Storage should be in accordance with national regulations for radioactive materials.

6.5. **Nature and content of container**

a) 15 mL, type I Ph. Eur. clear, colourless glass vial, containing 1 mL of sterile solution; and

b) 15 mL, type I Ph. Eur. clear, colourless glass vial, containing a freeze-dried powder intended for reconstitution with the solution in vial (A) above and then labelled with Sodium Pertechnetate [99mTc] Solution Ph. Eur.

Pack size: Kit containing 5 vials A and 5 vials B.
6.6. Instructions for use, handling and disposal

The product is to be used after reconstitution of the kit and labelling with addition of sodium pertechnetate \([99m\text{Tc}]\) solution for injection, allowing the preparation of technetium \([99m\text{Tc}]\) colloidal rhenium sulphide injection (Nanocolloid).

The mean diameter of the colloidal particles is around 100 nm (Brownian notion and Photon correlation spectroscopy measuring principles).

Method of preparation

Usual precautions regarding sterility and radioprotection should be respected.

Take a vial B from the kit and introduce through the asepticized rubber cap 2 mL of water for injection with a hypodermic syringe (do not use a breather needle). Shake the vial to dissolve the product.

Introduce without breather needle 0.5 mL of solution from the vial B into a vial A. Shake.

Put vial A in an appropriate lead shielding. Introduce without breather needle 1 to 2 mL of \([99m\text{Tc}]\) sodium pertechnetate injection with an activity of 370 to 5550 MBq.

Put vial A in a boiling water-bath during 15 to 30 minutes without lead shielding.

Cool the vial under running water.

Quality control

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

Method

Ascending paper chromatography

Materials and reagents

1. Chromatographic paper
   Whatman 1 strip of sufficient length and not less than 2.5 cm wide.
   Trace at 2 cm from one of the ends of the paper strip a fine line called "deposit line" and an other line called "front line" at 10 cm from the "deposit line".

2. Mobile phase
   Methylethylketone

3. Glass tank
   Glass tank of suitable size for the chromatographic paper used, ground at the top to take a closely fitting lid. In the top of the tank is a device which suspends the chromatographic paper and is capable of being lowered without opening the chamber.

4. Miscellaneous
   Forceps, scissors, syringes, needles, appropriate counting assembly.
Procedure

The method of preparation of the kit is described above § 6.6.

1. Place into the glass tank a layer 2 cm deep of the mobile phase.

2. Remove a spot of the preparation and apply it to the "deposit line" of the paper strip using a syringe and needle and dry in air.

3. Using forceps, insert the paper strip into the tank and close the lid. Lower the paper into the mobile phase and allow the solvent to migrate until the "front line".

4. Remove the paper strip with forceps and dry in air.

5. Determine distribution of activity with an appropriate detector. Identify each radioactive spot by calculating the Rf. The Rf of technetium $^{99m}$Tc complex is 0, and that of impurities ($^{99m}$Tc pertechnetate) is 1. Measure the activity of each spot by integration of the peaks.

6. Calculations
   Calculate the percentage of technetium $^{99m}$Tc complex (radiochemical purity)

   \[
   \% \text{ technetium } ^{99m}\text{Tc} \text{ complex} = \frac{\text{Activity of the spot at Rf 0}}{\text{Total Activity of the paper strip}} \times 100
   \]

   Calculate the percentage of impurities

   \[
   \% \text{ of impurities} = \frac{\text{Activity of the spot at Rf 1}}{\text{Total activity of the paper strip}} \times 100
   \]

7. The percentage of technetium $^{99m}$Tc complex (radiochemical purity) should be at least 95 % and the percentage of impurities should not be greater than 5 %.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill or urine, vomiting, etc. Suitable precautions should be taken concerning the radioactivity eliminated by the patients in order to avoid any contamination. Radiation protection precautions in accordance with national regulations must therefore be taken.

The residues may be put in an ordinary waste bin so far as long as the activity of vials and syringes does not exceed that of background when measured with a low level radiation detector. Any unused product or waste material should be disposed of in accordance with local requirements.
7. **MARKETING AUTHORISATION HOLDER**
   
   CIS bio international  
   B.P. 32 - 91192 GIF-SUR-YVETTE CEDEX  
   FRANCE

8. **MARKETING AUTHORISATION NUMBER**
   
   Country specific.

9. **DATE OF FIRST AUTHORISATION / RENEWAL OF AUTHORISATION**
   
   Country specific.

10. **DATE OF REVISION OF TEXT**
    
    01/2007

**DENMARK**

Marketing authorisation number : DK R. 1042  
First authorisation : 31.01.1995  
Renewal of authorisation : 31.01.2005

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Marketing authorisation number : 11249  
First authorisation : 29.11.1993  
Renewal of authorisation : 05.01.2001

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First authorisation : 08.05.2001

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SWEDEN
Marketing authorisation number : 16241
First authorisation : 25.01.2002

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