Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Nanocis 0.24 mg kit for radiopharmaceutical preparation

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial A contains 0.24 mg of rhenium sulphide, corresponding to 0.15 mg of elemental rhenium.

The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
Powder and solvent for solution for injection, or for oral solution.

Vial A: Dark brown colloidal solution
Vial B: White, freeze-dried powder

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After labelling with sodium pertechnetate (^{99m}Tc) solution for injection:

- Lymphoscintigraphy for the purpose of visualising the regional lymphatic system:
. imaging and intraoperative detection of sentinel lymph nodein the following tumours: breast cancer, malignant melanoma, vulvar carcinoma, penile carcinoma, prostate cancer and head and neck squamous cell carcinoma.
. lymphatic flow scintigraphy for diagnosing lymphatic oedema in the limbs.

- Digestive exploration (gastroesophageal scintigraphy).

4.2 Posology and method of administration

Method of administration
Multidose vial.
This medicinal product should be reconstituted before administration to the patient.
For instructions on reconstitution of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.
Adults and elderly

Lymphoscintigraphy:

- **Imaging and detection of sentinel lymph node**

The activity of (^{99m}Tc) technetium colloidal rhenium sulphide in adults depends upon the indication, the anatomical region that is to be investigated and the time between the injection and imaging.
The injection site is selected according to the anatomical area to be investigated. The injection is made without pressure into loose connective tissue which should not be poorly vascularised. Before the injection, an aspiration test should ascertain that no blood vessel was inadvertently punctured.

Melanoma: 5-120 MBq intradermally in at least four depots (on the extremities only two) around the tumour/scar at a distance of 0.1–1 cm. The total activity to be injected must be divided into the number of aliquots to be injected around the tumour/scar according to the body location, It is recommended to not exceed 0.2 ml of volume for each site.
Lymphoscintigraphic images are obtained starting after the injection and regularly thereafter until the sentinel lymph node is visualised.

Breast cancer: 5 - 20 MBq (0.2 mL) divided into one or more injections under palpation or ultrasound. A maximum volume of 0.5 mL may be justified in cases of deep tumour.
In case of superficial tumor, route of administration may be either intradermal next to the tumor or subcutaneous peri-tumoral. The injection can be performed peri-areolar when tumour is in upper-quadrants.
In case of deep tumor, peri-tumor route of administration is recommended.
Scintigraphic scans of breast and axillary region can be acquired between 15 to 30 minutes and 3 hours after injection.

Prostate cancer: on the day before or on the day of surgery, 200 MBq through the rectum in prostate lobes under ultrasound (an injection of 100 MBq in 0.3 mL for each prostatic lobe). The patient has previously received prophylactic broad-spectrum antibiotic (as for any prostate biopsy).
The scintigraphic images are performed immediately after the patient has emptied his bladder.

Penile cancer: On the day before operation, 60 MBq is administered intradermally 2 cm proximal to the penile tumour.
Lymphoscintigraphic images are obtained starting after the injection and regularly thereafter until the sentinel lymph node is visualised.

Vulvar cancer: On the day before surgery, 0.2 mL with a 60-120 MBq activity is administered intradermally at four sites around the tumour.
Lymphoscintigraphic images are obtained starting after the injection and every 30 minutes thereafter until the sentinel lymph node is visualized.

Head and neck cancer: After the patient has received topical anaesthesia, 20-40 MBq in 0.5-1.0 mL is injected submucosally around the circumference of the tumour. A non-alcoholic mouthwash is used immediately after the injection to minimize the possibility that the patient might swallow residual radioactive material. Scintigraphy is performed immediately and up to 2 hours after injection.

- **Lymphatic flow scintigraphy**

20-200 MBq given by single or multiple subcutaneous injection(s). The activity is usually below 20 MBq per injection site, depending on the anatomical areas to be investigated and the time interval between injection and imaging. Recommended volumes are 0.2-0.3 mL. A maximum volume of 0.5 mL per injection site should not be exceeded.

Paediatric population
The activity to be administered in children should be a fraction of the adult activity and should be calculated according to the following equation:

$$\text{Paediatric activity (MBq)} = \frac{\text{Adult dose (MBq)} \times \text{child weight (kg)}}{70\ \text{(kg)}}$$

In a limited number of cases the body surface area may be considered to be more appropriate.

$$\text{Paediatric activity (MBq)} = \frac{\text{Adult dose (MBq)} \times \text{child surface (m}^2\text{)}}{1.73}$$

A minimum activity of about 5 – 10 MBq per injection site is, however, needed to achieve uptake of sufficient quality.

Study of the Gastro Oesophageal Reflux:

For adults, the patient receives an oral activity of 3.5 to 12 MBq of technetium (^{99m}Tc) colloidal rhenium sulphide (other activities may be justifiable) in a liquid phase in accordance with local practice.
Dynamic scintigraphy may be performed along with static imaging.

For children 3.5 to 12 MBq is given in a liquid phase according to local practice.

4.3 Contraindications

Hypersensitivity to the active substance, 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

Lymphoscintigraphy is not advised in patients with complete obstruction of the lymphatic system, 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.
For each patient, exposure to ionising radiation must be justifiable on the basis of likely benefits. 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 result.

Specific warnings
This medicinal product contains less than 1 mmol sodium (23 mg) per procedure, that is to say essentially 'sodium- free'.

The contents of NANOCIS are intended only for the preparation of technetium (^{99m}Tc) labelled solution for injection (see section 12). Unlabelled NANOCIS should not be administered to the patient.

Technetium (^{99m}Tc)-labelled NANOCIS must be handled with care and appropriate safety measures should be used to minimise radiation exposure to the patient and to the healthcare professionals (see section 11), consistent with proper patient management."

4.5 Interaction with other medicinal products and other forms of interactions

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

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When 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 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 foetus.

Breastfeeding
Before administering radiopharmaceuticals to a mother who is breastfeeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased 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 24 hours and the expressed feeds discarded.

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

In some cases, administration of the product can involve allergic side effects.

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

From Post-marketing surveillance, the following adverse events have been reported:

Immune system disorders Very rare	Hypersensitivity.
General disorders and administration site conditions Very rare	Pain.

The following presents how the frequencies are reflected in this section: Very rare (<1/10,000);

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.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance; Website: http://www.hpra.ie

4.9 Overdose

In the event of the administration of a radiation overdose after oral administration, the absorbed dose to the patient undergoing gastroesophageal scintigraphy can be reduced by increasing the elimination of the radionuclide from the body by using laxatives to promote faecal excretion.

In the event of the administration of a radiation overdose after subcutaneous injection, 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}Tc) colloidal rhenium sulphide does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

*** Subcutaneous injection:**
Technetium (^{99m}Tc) colloidal rhenium sulphide is administered by subcutaneous injection, in general in the region of the interdigital space of the hand or foot, or in the marginal area of a tumour.

The lymphatic capillaries have a discontinuous wall with pores and no basal membrane, so that colloids because of their small size can be rapidly taken up into the lymph capillaries from the interstitial fluid. During transport of the lymph through lymph nodes, some of the colloidal particles are phagocytosed by bordering cells of the reticuloendothelial system in the lymph nodes. This is repeated from one lymph node to the next.

The radiopharmaceutical preparation is a metal colloid, which is partly phagocytosed and stored in the first lymph node group.

Following injection, the activity in the lymph node corresponds to 3.06 ± 0.10 % of the administered activity at the first hour, and 3.83 ± 0.16 % at the third hour.

Passage into the blood vessels is insignificant during the first few hours after administration.

Experimental data show urinary and hepatic elimination of the injected product.
11 % of the injected activity is retrieved in the liver parenchyma after 3 hours. Urinary elimination gradually increases and reaches 14.6 % of the injected activity at one hour.

* **Administration *per os*:**
Technetium (^{99m}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 $Na_4P_2O_7$, 10 H_2O/kg.

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Vial A (under nitrogen atmosphere):

Gelatin
Ascorbic acid
Sodium hydroxide (for pH adjustment)
Concentrated hydrochloric acid
Water for injections

Vial B (under nitrogen atmosphere):

Stannous chloride dihydrate
Sodium pyrophosphate decahydrate
Sodium hydroxide (for pH adjustment)
Concentrated hydrochloric acid (for pH adjustment)

6.2 Incompatibilities

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

6.3 Shelf life

6 months

After reconstitution, do not store above 25°C and use within 4 hours.

6.4 Special precautions for storage

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

For storage conditions of the reconstituted 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

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 (^{99m}Tc) Solution Ph. Eur.

Pack size: Kit containing 5 vials A and 5 vials B.

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 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 vials is intended only for use in the preparation of technetium (^{99m}Tc) colloidal rhenium sulphide and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on reconstitution and radiolabelling of the medicinal product before administration, see section 12.

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.

All lumpectomy specimens should be stored for decontamination until the dose rate equals background levels.

The residues may be put in an ordinary waste bin 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 medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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

8 MARKETING AUTHORISATION NUMBER

PA0677/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 07 July 1999

Date of last renewal: 07 July 2009

10 DATE OF REVISION OF THE TEXT

October 2020

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 10^5 years, can be regarded as quasi stable.

*** Dosimetry data after subcutaneous administration:**

The absorbed radiation dose for a patient (70 kg body weight) after administration of technetium (^{99m}Tc) colloidal rhenium sulphide has been calculated using a dosimetric model assuming a subcutaneous injection in the breast and a lymphogenic outflow of 20 % of the activity.

Table 1: Absorbed radiation dose (mGy/MBq injected activity) and effective dose (mSv/MBq injected activity) after subcutaneous injection in the breast by gamma rays emanating from injections depot and by absorption in RES in case of lymphogenic outflow.**

Organ	Absorbed dose resulting from the subcutaneous injection depot (mGy/MBq)***	Absorbed dose per percentage of outflow mGy/MBq/% flow****	Total absorbed dose for injected activity of 200 MBq and assumption of lymphogenic outflow of 20 % *****
Breast	5.6 x 10^{-2}	2.58 x 10^{-5}	11.30
Heart	1.04 x 10^{-2}	8.36 x 10^{-5}	2.41
Thymus	9.94 x 10^{-3}	2.56 x 10^{-5}	2.09
Lungs	7.85 x 10^{-3}	7.70 x 10^{-5}	1.88
Bone surfaces	2.97 x 10^{-3}	1.10 x 10^{-4}	1.03
Skin	2.80 x 10^{-3}	1.53 x 10^{-5}	0.62
Liver	2.77 x 10^{-3}	8.91 x 10^{-4}	4.12
Stomach wall	2.49 x 10^{-3}	8.17 x 10^{-5}	0.82
Pancreas	2.34 x 10^{-3}	1.67 x 10^{-4}	1.14
Adrenal	1.88 x 10^{-3}	1.51 x 10^{-4}	0.98
Red bone marrow	1.85 x 10^{-3}	1.04 x 10^{-4}	0.79
Muscles	1.69 x 10^{-3}	3.30 x 10^{-5}	0.47
Spleen	1.61 x 10^{-3}	8.66 x 10^{-4}	3.79
Gallbladder	1.39 x 10^{-3}	2.40 x 10^{-4}	1.24
Thyroid gland	1.22 x 10^{-3}	1.02 x 10^{-5}	0.29
Kidneys	7.71 x 10^{-4}	1.14 x 10^{-4}	0.61
Upper large intestine	4.72 x 10^{-4}	6.84 x 10^{-5}	0.37
Small intestine	3.05 x 10^{-4}	5.07 x 10^{-5}	0.26
Uterus	1.21 x 10^{-4}	2.39 x 10^{-5}	0.12
Lower large intestine	1.13 x 10^{-4}	2.26 x 10^{-5}	0.11
Ovaries	1.11 x 10^{-4}	2.92 x 10^{-5}	0.14
Brain	1.02 x 10^{-4}	8.09 x 10^{-6}	0.05
Bladder wall	7.86 x 10^{-5}	1.27 x 10^{-5}	0.07
Testes*	0.10 x 10^{-4}	3.92 x 10^{-6}	0.02
Whole body	4.06 x 10^{-3}	6.13 x 10^{-5}	1.06

Effective dose (mSv)	**4.7 x 10^{-3}**	**9.59 x 10^{-5}**	**1.32**

* Testes values calculated as per "adult male model".
**: RES: reticulo-endothelial system
***: Absorbed dose per applied activity from the subcutaneous injection depot (mGy/MBq) with the hypothesis that the depot stays at the injection site.
****: Absorbed dose per percentage of outflowing colloid in the RES (mGy/MBq/% flow) with the hypothesis that the depot does not stay totally at the injection site but migrates to RES.
*****: Total absorbed dose as a total of column 1 and 2 for injected activity of 200 MBq and assumption of lymphogenic outflow of 20 %

After subcutaneous administration of 200 MBq (maximum activity) in adults and with an assumed lymphogenic outflow of 20%, the effective dose is 1.32 mSv.

The absorbed dose in the target organ (lymph nodes) mostly ranges from 100 to 400 mGy. Mean absorbed doses in the critical organs are: breast 11.30 mGy, liver 4.12 mGy, spleen 3.79 mGy, lungs 1.88 mGy, gallbladder 1.24 mGy, red bone marrow 0.79 mGy; kidneys 0.61 mGy, and bladder wall 0.07mGy.

Radiation exposure to healthcare professionals

The radiation exposure to operating room personnel, and pathologist during breast sentinel lymph nodebiopsy has been estimated after a peritumoral injection of 25 to 40 MBq in breast cancer of ^{99m}Tcsulphide colloid 1.5 to 3 hours before lumpectomy. The results are presented in the table below.

Table 2: radiation exposure to operating room personnel, and pathologist during breast sentinel lymph node biopsy

Operating room and pathologist exposure (mSv/h)			
	Breast injection site	Lumpectomy	Sentinel Lymph node
3 cm (surgeon's hands)	0.34 (0.20-0.42)	0.018	0.0006
30 cm (surgeon's torso)	0.013	0.003	0.0004
300 cm (scrub nurse's torso)	0.001	NA	NA
3 cm (pathologist's hands)		0.018	0.0006
30 cm (pathologist's torso)		0.003	0.0004

*** Dosimetry data on *per os* 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).

Table 3: Tc-LABELLED NON-ABSORBABLE MARKERS
Oral administration of fluids

Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	2.5 x 10^{-3}	3.3 x 10^{-3}	5.5 x 10^{-3}	8.9 x 10^{-3}	1.5 x 10^{-2}
Bladder	6.9 x 10^{-3}	9.1 x 10^{-3}	1.4 x 10^{-2}	2.2 x 10^{-2}	3.5 x 10^{-2}
Bone surfaces	4.2 x 10^{-3}	5.2 x 10^{-3}	7.4 x 10^{-3}	1.1 x 10^{-2}	2.1 x 10^{-2}
Brain	1.8 x 10^{-6}	3.4 x 10^{-6}	1.2 x 10^{-5}	4.0 x 10^{-5}	1.0 x 10^{-4}
Breast	2.8 x 10^{-4}	4.2 x 10^{-4}	9.4 x 10^{-4}	2.0 x 10^{-3}	3.8 x 10^{-3}
Gall bladder	1.4 x 10^{-2}	1.8 x 10^{-2}	3.0 x 10^{-2}	4.3 x 10^{-2}	7.1 x 10^{-2}

GI-tract					
Stomach	2.2×10^{-2}	2.9×10^{-2}	4.1×10^{-2}	6.6×10^{-2}	1.2×10^{-1}
SI	6.0×10^{-2}	7.6×10^{-2}	1.2×10^{-1}	1.9×10^{-1}	3.5×10^{-1}
Colon	1.0×10^{-1}	1.3×10^{-1}	2.2×10^{-1}	3.5×10^{-1}	6.6×10^{-1}
(ULI	1.2×10^{-1}	1.5×10^{-1}	2.5×10^{-1}	4.0×10^{-1}	7.5×10^{-1})
(LLI	8.3×10^{-2}	1.1×10^{-1}	1.8×10^{-1}	2.9×10^{-1}	5.4×10^{-1})
Heart	1.0×10^{-3}	1.4×10^{-3}	2.5×10^{-3}	4.3×10^{-3}	8.6×10^{-3}
Kidneys	5.5×10^{-3}	6.7×10^{-3}	1.0×10^{-2}	1.5×10^{-2}	2.3×10^{-2}
Liver	3.7×10^{-3}	4.8×10^{-3}	9.3×10^{-3}	1.5×10^{-2}	2.7×10^{-2}
Lungs	5.7×10^{-4}	9.1×10^{-4}	1.6×10^{-3}	2.9×10^{-3}	5.7×10^{-3}
Muscles	3.2×10^{-3}	4.0×10^{-3}	6.0×10^{-3}	9.0×10^{-3}	1.5×10^{-2}
Oesophagus	1.9×10^{-4}	3.0×10^{-4}	5.0×10^{-4}	1.2×10^{-3}	2.6×10^{-3}
Ovaries	2.5×10^{-2}	3.2×10^{-2}	4.8×10^{-2}	6.8×10^{-2}	1.1×10^{-1}
Pancreas	5.9×10^{-3}	7.9×10^{-3}	1.2×10^{-2}	1.8×10^{-2}	3.1×10^{-2}
Red marrow	4.7×10^{-3}	5.7×10^{-3}	7.5×10^{-3}	9.2×10^{-3}	1.1×10^{-2}
Skin	9.3×10^{-4}	1.1×10^{-3}	1.7×10^{-3}	2.9×10^{-3}	5.4×10^{-3}
Spleen	4.0×10^{-3}	5.0×10^{-3}	7.8×10^{-3}	1.2×10^{-2}	2.0×10^{-2}
Testes	1.3×10^{-3}	2.0×10^{-3}	3.8×10^{-3}	6.5×10^{-3}	1.2×10^{-2}
Thymus	1.9×10^{-4}	3.0×10^{-4}	5.0×10^{-4}	1.2×10^{-3}	2.6×10^{-3}
Thyroid	2.0×10^{-5}	4.8×10^{-5}	1.5×10^{-4}	3.0×10^{-4}	1.2×10^{-3}
Uterus	1.6×10^{-2}	2.0×10^{-2}	3.1×10^{-2}	4.7×10^{-2}	7.6×10^{-2}
Remaining organs	5.2×10^{-3}	7.2×10^{-3}	1.1×10^{-2}	2.0×10^{-2}	3.0×10^{-2}
Effective dose (mSv/MBq)	1.9×10^{-2}	2.5×10^{-2}	3.9×10^{-2}	6.2×10^{-2}	1.1×10^{-1}

For this product the effective dose resulting from a *per os* administered activity of 12 MBq is typically 0.23 mSv (per 70 kg individual).

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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

Usual precautions regarding sterility and radioprotection should be respected.

The heating block used must be adapted to the size of the vial to allow an optimal temperature rise at 100°C in the labelling vial.

Make sure that the water bath (or the heating block) is in equilibrium to allow a temperature of 100 °C in the labelling vial.

Do not use any venting needle. The freeze-dried product is under nitrogen atmosphere. The product must not be in contact with air.

The water for injection used should be taken from a freshly opened bottle.
The product is to be used after reconstitution of the kit and labelling with addition of sodium pertechnetate (^{99m}Tc) solution for injection, allowing the preparation of technetium (^{99m}Tc) colloidal rhenium sulphide injection (Nanocolloid).
Pertechnetate (^{99m}Tc) solution for injection should have been freshly eluted.

Method of preparation

1. Take a vial B from the kit and introduce through the previously disinfected rubber cap 2 ml of water for injection with a hypodermic syringe without refitting the plunger of the syringe after the addition. Shake the vial until complete dissolution of

the powder.
2. Introduce 0.5 ml of solution from vial B into a vial A. Before removing the syringe from the vial, withdraw the same volume (0.5 mL) of gas from this vial A.
Shake.

3. Put vial A in an appropriate lead shielding. Introduce 1 to 2 ml of sodium pertechnetate (^{99m}Tc) injection with an activity the range of 370 to 5550 MBq.
Before removing the syringe from the vial, withdraw the same volume of gas as the volume of solution added from the above solution.

4. Put vial A without the lead shielding in a heating block at 105°C or in a boiling water-bath for **30 minutes**.
Then, cool the vial under running water.

The suspension of technetium (^{99m}Tc)- colloidal rhenium sulphide obtained is a dark brown suspension, free from visible particles with a pH ranging between 4.5 and 6.5.

Quality control

The quality of labelling (radiochemical purity) can be checked according to the following procedure.
A suitability test allowing to check the migration of (^{99m}Tc) pertechnetate can be also performed in the same quality control conditions.

The methyl ethyl ketone saturation chromatography tank should be **prepared the same day.**

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 of one of the ends of the paper strip a fine line called "deposit line" and another 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 radiolabelled suspension is described above.

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

2. Using a syringe and needle, apply a sample of the prepared suspension at the "deposit line". **Do not allow the spot to dry.**

3. Using forceps, place the strip in the chromatography tank **immediately** and replace the cover. Lower the paper into the mobile phase and allow the solvent to migrate until the "front line".

4. Remove the paper strip from the tank with forceps and allow it to dry.

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 %.

Suitability test

1. On another strip, apply a droplet (1 to 5 µL) of ^{99m}Tc pertechnetate used for the radiolabelling
2. Perform the quality control test as defined upper for the prepared suspension.
3. The radio chromatogram should have a radioactive spot with Rf between 0.9 and 1 representing at least 95% of the activity. It should not have a radioactive spot with Rf 0-0.1 representing more than 5% of the activity.

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