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Guideline on core SmPC and Package Leaflet for technetium (99mTc) sestamibi

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Executive summary

This guideline describes the information to be included in the Summary of Products Characteristics (SmPC) and Package Leaflet for technetium (99mTc) sestamibi.

1. Introduction (background)

The purpose of this core SmPC and Package Leaflet is to provide applicants and regulators with harmonised guidance on the information to be included in the Summary of Product Characteristics (SmPC) for technetium (99mTc) sestamibi1. This guideline should be read in conjunction with the core SmPC and Package Leaflet for Radiopharmaceuticals, the QRD product information templates and the guideline on Summary of Product Characteristics.

This Core SmPC has been prepared on the basis, and taking into account the available published scientific literature dated from more than 10 years. However, any new application for a kit for radiopharmaceutical preparation composed of technetium (99mTc) sestamibi should be submitted with all the needed and adequate data in order to be valid.

The activities to be administered to children and to adolescents may be calculated according to the EANM Dosage Card [Lassmann M et al. Eur J Nucl Med Mol Imaging (2008) 35:1667].

2. Scope

This core SmPC and Package Leaflet covers technetium (99mTc) sestamibi.

3. Legal basis

This guideline has to be read in conjunction with Article 11 of Directive 2001/83 as amended, and the introduction and general principles (4) and part I of the Annex I to Directive 2001/83 as amended.

4. Core SmPC and Package Leaflet for technetium (^{99m}Tc) sestamibi

[1] Concept paper on the harmonisation and update of the clinical aspects in the authorised conditions of use for radiopharmaceuticals and other diagnostic medicinal products (EMEA/CHMP/EWP/12052/2008)

Core SmPC and Package Leaflet for technetium (^{99m}Tc) sestamibi

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

<▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.>

1. NAME OF THE MEDICINAL PRODUCT

{(Invented) name strength pharmaceutical form}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains [...] mg [tetrakis (1 isocyanide-2-methoxy-2-methylpropyl-)copper(I)] tetrafluoroborate. The radionuclide is not part of the kit.

<Excipient(s) with known effect:>
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

[Appearance product specific]

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only. This is indicated for adults. For paediatric population see section 4.2.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of technetium (^{99m}Tc) sestamibi obtained is indicated for:

- Myocardial perfusion scintigraphy
  for the detection and localisation of coronary artery disease (angina pectoris and myocardial infarction)
- Assessment of global ventricular function. First-pass technique for determination of ejection fraction and/or ECG-triggered, gated SPECT for evaluation of left ventricular ejection fraction, volumes and regional wall motion.
- Scintimammography for the detection of suspected breast cancer when mammography is equivocal, inadequate or indeterminate.
- Localisation of hyperfunctioning parathyroid tissue in patients with recurrent or persistent disease in both primary and secondary hyperparathyroidism, and in patients with primary hyperparathyroidism scheduled to undergo initial surgery of the parathyroid glands.

4.2 Posology and method of administration

Posology

Adults and elderly population

Posology may vary depending on gamma camera characteristics and reconstruction modalities. The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.

The recommended activity range for intravenous administration to an adult patient of average weight (70 kg) is for:

Diagnosis of reduced coronary perfusion and myocardial infarction

400 – 900 MBq

The recommended activity range for diagnosis of ischaemic heart disease according to the European procedural guideline is

– Two-day protocol: 600–900 MBq/study
– One-day protocol: 400–500 MBq for the first injection, three times more for the second injection.

Not more than a total of 2000 MBq should be administered for a one-day protocol and 1800 MBq for a two-day-protocol. For a one day protocol, the two injections (stress and rest) should be done at least two hours apart but may be performed in either order. After the stress injection, exercise should be encouraged for an additional one minute (if possible).

For diagnosis of myocardial infarction one injection at rest is usually sufficient.

For diagnosis of ischaemic heart disease two injections (stress and rest) are required in order to differentiate transiently from persistently reduced myocardial uptake.

Assessment of global ventricular function

600-800 MBq injected as a bolus.

Scintimammography

700 - 1000 MBq injected as a bolus usually in the arm opposite to the lesion.

Localisation of hyperfunctioning parathyroid tissue

200 - 700 MBq injected as a bolus. The typical activity is between 500-700 MBq.

Posology may vary depending on gamma camera characteristics and reconstruction modalities.

The injection of activities greater than local DRLs (Diagnostic Reference Levels) should be justified.

Renal impairment
Careful consideration of the activity to be administered is required since an increased radiation exposure is possible in these patients.

Hepatic impairment
In general, activity selection for patients with a decreased hepatic function should be cautious, usually starting at the low end of the dosing range.

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 adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.
A[MBq]Administered = Baseline Activity × Multiple

The baseline activity is 63 MBq as a cancer seeking agent. For cardiac imaging, the minimum and maximum baseline activities are 42 and 63 MBq, respectively, for the two-day protocol cardiac scan both at rest and stress. For the one-day cardiac imaging protocol, the baseline activity is 28 MBq at rest and 84 MBq at stress. The minimum activity for any imaging study is 80 MBq.

Weight [kg]	Multiple	**Weight [kg**	Multiple	**Weight [kg]**	Multiple
3	1	22	5.29	**42**	9.14
4	1.14	**24**	5.71	**44**	9.57
6	1.71	**26**	6.14	**46**	10.00
8	2.14	**28**	6.43	**48**	10.29
10	2.71	**30**	6.86	**50**	10.71
12	3.14	**32**	7.29	**52-54**	11.29
14	3.57	**34**	7.72	**56-58**	12.00
16	4.00	**36**	8.00	**60-62**	12.71
18	4.43	**38**	8.43	**64-66**	13.43
20	4.86	**40**	8.86	**68**	14.00

Method of administration
For intravenous use.
Because of potential tissue damage, extravasal injection of this radioactive product has to be strictly avoided.
For <multidose> <single dose> use.

Precautions to be taken before handling or administration of the medicinal product
This medicinal product should be reconstituted before administration to the patient. For instructions on reconstitution and control of the radiochemical purity of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4.

Image acquisition

Cardiac imaging
Imaging should begin approximately after 30-60 min after injection to allow for hepatobiliary clearance. Longer delay can be required for resting images and for stress with vasodilatators alone because of the risk of higher subdiaphragmatic technetium (^{99m}Tc) activity. There is no evidence for significant changes in myocardial tracer concentration or redistribution, therefore imaging for up to 6 hours post injection is possible. Test may be done in a one day or two days protocol.

Preferably tomographic imaging (SPECT) with or without ECG gating should be performed.

Scintimammography
Breast imaging is optimally initiated 5 to 10 minutes post injection with the patient in the prone position with breast freely pendant.

The product is administered in an arm vein contralateral to the breast with the suspected abnormality. If the disease is bilateral, the injection is ideally administered in a dorsal vein of the foot.

Conventional gamma camera
The patient should then be repositioned so that the contralateral breast is pendant and a lateral image of it should be obtained. An anterior supine image may then be obtained with the patient's arms behind her head.

Detector dedicated to breast imaging
In case a detector dedicated to breast imaging is used, a relevant machine-specific protocol must be followed to obtain the best possible imaging performance.

Parathyroid imaging
Parathyroid image acquisition depends on the protocol chosen. The most used studies are either the subtraction and/or the dual-phase techniques, which can be performed together.

For the subtraction technique either sodium iodide (^{123}I) or sodium pertechnetate (^{99m}Tc) can be used for imaging for the thyroid gland since these radiopharmaceuticals are trapped by functioning thyroid tissue. This image is subtracted from the technetium (^{99m}Tc) sestamibi image, and pathological hyperfunctioning parathyroid tissue remains visible after subtraction. When sodium iodide (^{123}I) is used, 10 to 20 MBq are orally administered. Four hours after the administration, neck and thorax images may be obtained. After sodium iodide (^{123}I) image acquisition, 200 to 700 MBq of technetium (^{99m}Tc) sestamibi are injected and images are acquired 10 minutes post injection in double acquisition"with 2 peaks of gamma energy (140 keV for technetium (^{99m}Tc) and 159 keV for iodine (^{123}I)). When sodium pertechnetate (^{99m}Tc) is used, 40-150 MBq are injected and neck and thorax images are acquired 30 minutes later. Then 200 to 700 MBq of technetium (^{99m}Tc) sestamibi are injected and a second acquisition of images is acquired 10 minutes later.

For the dual phase technique is used, 400 to 700 MBq of technetium (^{99m}Tc) sestamibi are injected and the first neck and mediastinum image is obtained 10 minutes later. After a wash-out period of 1 to 2 hours, neck and mediastinum imaging is again performed.

The planar images may be complemented by early and delayed SPECT or SPECT/CT.

4.3 Contraindications

Hypersensitivity to the active substance(s), to any of the excipients listed in section 6.1 <or {name of the residue(s)}> <or to any of the components of the labelled radiopharmaceutical.>

In myocardial scintigraphy investigations under stress conditions, the general contraindications associated with the induction of ergometric or pharmacological stress should be considered.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
If hypersensitivity or anaphylactic reactions occurs, 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 or hepatic impairment
Careful consideration of the benefit risk ratio in these patients is required since an increased radiation exposure is possible (see section 4.2).

Paediatric population
For information on the use in paediatric population, see section 4.2 <or 5.1>.
Careful consideration of the indication is required since the effective dose per MBq is higher than in adults (see section 11).

Patient preparation
The patient should be well hydrated before the start of the examination and urged to void as often as

possible during the first hours after the examination in order to reduce radiation.

Cardiac imaging
If possible, patients should fast for at least four hours prior to the study. It is recommended that patients eat a light fatty meal or drink a glass or two of milk after each injection, prior to imaging. This will promote rapid hepatobiliary clearance of technetium (^{99m}Tc) sestamibi resulting in less liver activity in the image.

Interpretation of technetium (^{99m}Tc) sestamibi images

Interpretation of scintimmamography
Breast lesions less than 1 cm in diameter may not all be detected with scintimammography as the sensitivity of technetium (^{99m}Tc) sestamibi for the detection of these lesions is low. A negative examination does not exclude breast cancer especially in such a small lesion.

After the procedure
Close contact with infants and pregnant women should be restricted during the initial 24 hours following the injection.

Specific warnings
In myocardial scintigraphy investigations under stress conditions, the general contraindications and precautions associated with the induction of ergometric or pharmacological stress should be considered.

<This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium-free'.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. This should be taken into account in patient on low sodium diet.>

For precautions with respect to environmental hazard see section 6.6.

4.5 Interaction with other medicinal products and other forms of interaction

Medicinal products which affect myocardial function and/or blood flow may cause false negative results in the diagnosis of coronary arterial disease. Particularly beta-blockers and calcium antagonists reduce oxygen consumption and thus also affect perfusion and beta-blockers inhibit the increase of heart frequency and blood pressure under stress. For this reason, concomitant medicinal product should be taken into consideration when interpreting the results of the scintigraphic examination. The recommendations of the applicable guidelines on ergometric or pharmacological stress tests should be followed.

When the subtraction technique is used for imaging of hyperfunctioning parathyroid tissue, recent use of iodine containing radiologic contrast media, medicinal products used to treat hyper- or hypothyroidism or of several other medicinal products is likely to decrease the quality of thyroid imaging and even makes subtraction impossible. For a complete list of possibly interacting medicinal products refer to the SmPCs of sodium iodide (^{123}I) or sodium pertechnetate (^{99m}Tc) .

Paediatric population
Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential
When an administration of radiopharmaceuticals to a woman of childbearing potential is intended, it is important to determine whether or not she is pregnant. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. If in doubt about her potential pregnancy (if the woman has missed a period, if the period is very irregular, etc.), alternative techniques not using ionising radiation (if there are any) should be offered to the patient.

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

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 breastfeeding, 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, breastfeeding should be interrupted for 24 hours and the expressed feeds discarded.

Close contact with infants should be restricted during the initial 24 hours following injection.

Fertility
No studies on fertility have been performed.

4.7 Effects on ability to drive and use machines

{Invented name} has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

The following table presents how the frequencies are reflected in this section:

Very common (≥1/10)
Common (≥1/100 to <1/10)
Uncommon (≥1/1,000 to <1/100)
Rare (≥1/10,000 to <1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

Immune system disorders
Rare: Severe hypersensitivity reactions such as dyspnoea, hypotension, bradycardia, asthenia and vomiting (usually within two hours of administration), angioedema. Other hypersensitivity reactions (allergic skin and mucosa reactions with exanthema (pruritus, urticaria, oedema), vasodilatation).
Very rare: Other hypersensitivity reactions have been described in predisposed patients.

Nervous system disorders
Uncommon: Headache
Rare: Seizures (shortly after administration), syncope.

Cardiac disorders
Uncommon: Chest pain/angina pectoris, abnormal ECG.
Rare: Arrhythmia.

Gastrointestinal disorders
Uncommon: Nausea
Rare: Abdominal pain.

Skin and subcutaneous tissue disorders
Rare: local reactions at the injection site, hypoaesthesia and paraesthesia, flushing.

Not known: Erythema multiform.

General disorders and administration site conditions
Common: Immediately after injection, a metallic or bitter taste, partly in combination with dry mouth and an alteration in the sense of smell may be observed.
Rare: Fever, fatigue, dizziness, transient arthritic-like pain, dyspepsia.

Other disorders
Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 16.4 mSv when the maximal recommended activity of 2000 MBq (500 at rest and 1500 MBq at stress) for a 1-day-protocol is administered these adverse reactions are expected to occur with a low probability.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

In the event of administration of a radiation overdose with technetium (^{99m}Tc) sestamibi the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition and defaecation. It might be helpful to estimate the effective dose that was applied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceuticals, Technetium (^{99m}Tc) compounds, ATC code: V09GA01.

Pharmacodynamic effects
At the chemical concentrations used for diagnostic examinations, technetium (^{99m}Tc) sestamibi solution does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

After reconstitution with sodium pertechnetate (^{99m}Tc), the following technetium (^{99m}Tc) sestamibi complex is formed:

$[^{99m}Tc\ (MIBI)_6]^+$ Where : MIBI = 2-methoxyisobutylisonitrile

Biodistribution
Technetium (^{99m}Tc) sestamibi from the blood is rapidly distributed into the tissue: 5 minutes after injection only about 8% of the injected dose remains in the blood pool. In physiological distribution, evident concentration of technetium (^{99m}Tc) sestamibi can be seen in vivo in several organs. In particular, normal tracer uptake is evident in the salivary glands, thyroid, myocardium, liver, gallbladder, small and large intestine, kidneys, bladder, choroid plexuses and skeletal muscles, occasionally in the nipples. Faint homogeneous uptake in the breast or axilla is normal.

Myocardial perfusion scintigraphy
Technetium (^{99m}Tc) sestamibi is a cationic complex which diffuses passively through the capillary and cell membrane. Within the cell it is localised in the mitochondria, where it is trapped, and retention is based on intact mitochondria, reflecting viable myocytes. After intravenous injection, it is distributed within the myocardium according to myocardial perfusion and viability. Myocardial uptake which is coronary flow

dependent is 1.5% of the injected dose at stress and 1.2% of the injected dose at rest. Irreversibly damaged cells however do not take up technetium (^{99m}Tc) sestamibi. The myocardial extraction level is reduced by hypoxia. It has very little redistribution and so separate injections are required for stress and resting studies.

Scintimammography
The tissue uptake of technetium (^{99m}Tc) sestamibi depends primarily on the vascularisation which is generally increased in tumor tissue. Technetium (^{99m}Tc) sestamibi accumulates in various neoplasms and most markedly in mitochondria. Its uptake is related to increased energy-dependent metabolism and cell proliferation. Its cellular accumulation is reduced when multidrug resistance proteins are overexpressed.

Parathyroid imaging of hyperfunctioning tissue
Technetium (^{99m}Tc) sestamibi localises in both parathyroid tissue and functioning thyroid tissue but usually washes out of normal thyroid tissue more rapidly than out of abnormal parathyroid tissue.

Elimination
Elimination of technetium (^{99m}Tc) sestamibi occurs mostly through the kidneys and the hepatobiliary system. Activity of technetium (^{99m}Tc) sestamibi from the gallbladder appears in the intestine within one hour of injection. About 27% of the injected dose is cleared through renal elimination after 24 hours and approximately 33% of the injected dose is cleared through the faeces in 48 hours. The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.

Half-life
The biological myocardial half-life of technetium (^{99m}Tc) sestamibi is approximately 7 hours at rest and stress. The effective half-life (which includes biological and physical half-lives) is approximately 3 hours for the heart and approximately 30 minutes for the liver.

5.3 Preclinical safety data

In acute intravenous toxicity studies in mice, rats and dogs, the lowest dose of the reconstituted kit that resulted in any deaths was 7 mg/kg (expressed as Cu $(MIBI)_4$ BF_4 content) in female rats. This corresponds to 500 times the maximal human dose (MHD) of 0.014 mg/kg for adults (70 kg). Neither rats nor dogs exhibited treatment related effects at reconstituted kit doses of 0.42 mg/kg (30 times MHD) and 0.07 mg/kg (5 times MHD) respectively for 28 days. At repeated dose administration, the first toxicity symptoms appeared during the administration of 150 times the daily dose during 28 days.

Extravasation administration in animals showed acute inflammation with oedema and haemorrhages at the injected site.

Studies on reproductive toxicity have not been conducted.

Cu $(MIBI)_4$ BF_4 showed no genotoxic activity in the Ames, CHO/HPRT and sister chromatid exchange tests. At cytotoxic concentrations, an increase in chromosome aberration was observed in the in vitro human lymphocyte assay. No genotoxic activity was observed in the in vivo mouse micronucleus test at 9 mg/kg.

Studies to assess the carcinogenic potential of the radiopharmaceutical kit have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

[Product specific]

6.2 Incompatibilities

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

6.3 Shelf life

[Product specific]
After radiolabelling: [...] hours. Do not store above [...]°C after radiolabelling.

6.4 Special precautions for storage

Do not store above [...]°C. Keep the vials in the outer carton in order to protect from light.
For storage conditions after radiolabelling of the medicinal product, see section 6.3.

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

6.5 Nature and contents of container

[Product specific]

6.6 Special precautions for disposal and other handling

General warnings
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licences 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.

Contents of the vial are intended only for use in the preparation of technetium (^{99m}Tc) sestamibi and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on extemporary preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory.

The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc), is added, adequate shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting or any other biological fluids. 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

{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

<Date of first authorisation: {DD month YYYY}>
<Date of latest renewal: {DD month YYYY}>

10. DATE OF REVISION OF THE TEXT

<{MM/YYYY}>
<{DD/MM/YYYY}>
<{DD month YYYY}>

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) generator and decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6.02 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13×10^5 years, can be regarded as quasi stable.

The data listed below are from ICRP 80 and are calculated according to the following assumptions. After intravenous injection, the substance is rapidly cleared from the blood and taken up predominantly mainly in muscular tissues (including heart), liver, and kidneys, with a smaller amount in salivary glands and thyroid. When the substance is injected in conjunction with a stress test, there is a considerable increase of the uptake in heart and skeletal muscles, with a correspondingly lower uptake in all other organs and tissues. The substance is excreted by the liver and kidneys in the proportions 75% and 25%, respectively.

	Absorbed dose per unit activity administered (mGy/MBq) (Resting subject)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0075	0.0099	0.015	0.022	0.038
Bladder	0.011	0.014	0.019	0.023	0.041
Bone surfaces	0.0082	0.010	0.016	0.021	0.038
Brain	0.0052	0.0071	0.011	0.016	0.027
Breast	0.0038	0.0053	0.0071	0.011	0.020
Gall bladder	0.039	0.045	0.058	0.1	0.32
Gastrointestinal tract					
Stomach	0.0065	0.0090	0.015	0.021	0.035
Small intestine	0.015	0.018	0.029	0.045	0.080

Colon	0.024	0.031	0.050	0.079	0.015
(Upper large intestine	0.027	0.035	0.057	0.089	0.17)
(Lower large intestine	0.019	0.025	0.041	0.065	0.12)
Heart	0.0063	0.0082	0.012	0.018	0.030
Kidneys	0.036	0.043	0.059	0.085	0.15
Liver	0.011	0.014	0.021	0.030	0.052
Lungs	0.0046	0.0064	0.0097	0.014	0.025
Muscles	0.0029	0.0037	0.0054	0.0076	0.014
Oesophagus	0.0041	0.0057	0.0086	0.013	0.023
Ovaries	0.0091	0.012	0.018	0.025	0.045
Pancreas	0.0077	0.010	0.016	0.024	0.039
Red marrow	0.0055	0.0071	0.011	0.030	0.044
Salivary glands	0.014	0.017	0.022	0.015	0.026
Skin	0.0031	0.0041	0.0064	0.0098	0.019
Spleen	0.0065	0.0086	0.014	0.020	0.034
Testes	0.0038	0.0050	0.0075	0.011	0.021
Thymus	0.0041	0.0057	0.0086	0.013	0.023
Thyroid	0.0053	0.0079	0.012	0.024	0.045
Uterus	0.0078	0.010	0.015	0.022	0.038
Remaining organs	0.0031	0.0039	0.0060	0.0088	0.016
Effective dose (mSv/MBq)	**0.0090**	**0.012**	**0.018**	**0.028**	**0.053**

	Absorbed dose per unit activity administered (mGy/MBq) (Exercise)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0066	0.0087	0.013	0.019	0.033
Bladder	0.0098	0.013	0.017	0.021	0.038
Bone surfaces	0.0078	0.0097	0.014	0.020	0.036
Brain	0.0044	0.0060	0.0093	0.014	0.023
Breast	0.0034	0.0047	0.0062	0.0097	0.018
Gall bladder	0.033	0.038	0.049	0.086	0.26
Gastrointestinal tract					
Stomach	0.0059	0.0081	0.013	0.019	0.032
Small intestine	0.012	0.015	0.024	0.037	0.066
Colon	0.019	0.025	0.041	0.064	0.12
(Upper large intestine	0.022	0.028	0.046	0.072	0.13)
(Lower large intestine	0.016	0.021	0.034	0.053	0.099)
Heart	0.0072	0.0094	0.010	0.021	0.035
Kidneys	0.026	0.032	0.044	0.063	0.11
Liver	0.0092	0.012	0.018	0.025	0.044
Lungs	0.0044	0.0060	0.0087	0.013	0.023
Muscles	0.0032	0.0041	0.0060	0.0090	0.017

Oesophagus	0.0040	0.0055	0.0080	0.012	0.023
Ovaries	0.0081	0.011	0.015	0.023	0.040
Pancreas	0.0069	0.0091	0.014	0.021	0.035
Red marrow	0.0050	0.0064	0.0095	0.013	0.023
Salivary glands	0.0092	0.011	0.0015	0.0020	0.0029
Skin	0.0029	0.0037	0.0058	0.0090	0.017
Spleen	0.0058	0.0076	0.012	0.017	0.030
Testes	0.0037	0.0048	0.0071	0.011	0.020
Thymus	0.0040	0.0055	0.0080	0.012	0.023
Thyroid	0.0044	0.0064	0.0099	0.019	0.035
Uterus	0.0072	0.0093	0.014	0.020	0.035
Remaining organs	0.0033	0.0043	0.0064	0.0098	0.018
Effective dose (mSv/MBq)	**0.0079**	**0.010**	**0.016**	**0.023**	**0.045**

The effective dose has been calculated according to a voiding frequency of 3.5 hours in adults.

Cardiac imaging
The effective dose resulting from the administration of a maximal recommended activity of 2,000 MBq of technetium (^{99m}Tc) sestamibi for an adult weighing 70 kg is about 16.4 mSv if implementing the one-day protocol with administration of 500 MBq at rest and 1,500 MBq at exercise.
For this administered activity of 2,000 MBq the typical radiation dose to the target organ heart is 14 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 69, 57 and 46.5 mGy, respectively.

The effective dose resulting from the administration of a maximal recommended activity of 1,800 MBq (900 MBq at rest and 900 MBq at exercise) of technetium (^{99m}Tc) sestamibi for a two-day protocol for an adult weighing 70 kg is about 15.2 mSv.
For this administered activity of 1,800 MBq the typical radiation dose to the target organ heart is 12.2 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 64.8, 55.8 and 44.1 mGy, respectively.

Scintimammography
The effective dose resulting from the administration of a maximal recommended activity of 1,000 MBq of technetium (^{99m}Tc) sestamibi for an adult weighing 70 kg is about 9 mSv.
For an administered activity of 1,000 MBq the typical radiation dose to the target organ breast is 3.8 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 39, 36 and 27 mGy, respectively.

Parathyroid imaging
The effective dose resulting from the administration of a maximal recommended activity of 700 MBq of technetium (^{99m}Tc) sestamibi for an adult weighing 70 kg is about 6.3 mSv.
For an administered activity of 700 MBq the typical radiation dose to the target organ thyroide is 3.7 mGy and the typical radiation doses to the critical organs gall bladder, kidneys and upper large intestine are 27.3, 25.2 and 18.9 mGy, respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened before disinfecting the stopper, the solution should be withdrawn via the stopper using a single dose syringe fitted

with suitable protective shielding and a disposable sterile needle or using an authorised automated application system.
If the integrity of this vial is compromised, the product should not be used

Instructions for preparation of technetium (^{99m}Tc) sestamibi
[Product specific]

Method of preparation
[Product specific]

Quality control
[Product specific]

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

{(Invented) name strength pharmaceutical form}
[Tetrakis(1-isocyanide-2-methoxy-2-methylpropy)copper(I)] tetrafluoroborate

< ▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.>

Read all of this leaflet carefully before you are given this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your nuclear medicine doctor who will supervise the procedure.
- If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What X is and what it is used for

This medicine is a radiopharmaceutical product for diagnostic use only.

X contains a substance called [tetrakis(1-isocyanide-2-methoxy-2-methylpropy)copper(I)] tetrafluoroborate which is used to study the heart function and blood flow (myocardial perfusion) by making an image of the heart (scintigraphy), for example in the detection of heart attacks (myocardial infarctions) or when a disease causes reduced blood supply to (a part of) the heart muscle (ischaemia). X is also used in the diagnosis of breast abnormalities in addition to other diagnostic methods when the results are unclear. X can also be used to find the position of overactive parathyroid glands (glands that secrete the hormone that controls blood calcium levels).

After X is injected, it temporarily collects in certain parts of the body. This radiopharmaceutical substance contains a small amount of radioactivity, which can be detected from outside of the body by using special cameras. You nuclear medicine doctor will then take an image (scintigraphy) of the concerned organ which can give your doctor valuable information about the structure and the function of this organ or the location of e.g., a tumour.

The use of X does involve exposure to small amounts of radioactivity. Your doctor and the nuclear medicine doctor have considered that the clinical benefit that you will obtain from the procedure with the radiopharmaceutical outweighs the risk due to radiation.

2. What you need to know before X is used

X must not be used
- if you are allergic to tetrakis (1 isocyanide-2-methoxy-2-methylpropyl-) copper(I)] tetrafluoroborate or any of the other ingredients of this medicine (listed in section 6).

Warnings and precautions
Take special care with X
- if you are pregnant or believe you may be pregnant,
- if you are breastfeeding,
- if you have a kidney or liver disease.

You should inform your nuclear medicine doctor in case those apply to you. You nuclear medicine doctor will inform you if you need to take any special precautions after using this medicine. Talk to your nuclear medicine doctor if you have any questions.

Before administration of X you should
- be fasting for at least 4 hours if the product is going to be used to perform images of your heart,
- drink plenty of water before the start of the examination in order to urinate as often as possible during the first hours after the study.

Children and adolescents
Talk to your nuclear medicine doctor <if you are under 18 years old>.

Other medicines and X
A number of medicines, foods and beverages can adversely affect the outcome of the planned investigation. It is therefore recommended to discuss with the referring physician, which intake should be discontinued before the investigation and when the medicines should be taken again. Tell also your nuclear medicine doctor if you are taking, have recently taken or might take any other medicines, since they may interfere with the interpretation of the images.
Especially tell your nuclear medicine doctor if you are taking medicines which affect heart function and/or blood flow.

Please ask your nuclear medicine doctor before taking any medicines.

Pregnancy and breast-feeding
You must inform the nuclear medicine doctor before the administration of X if there is a possibility you might be pregnant, if you have missed your period or if you are breast-feeding. When in doubt, it is important to consult your nuclear medicine doctor who will supervise the procedure.

If you are pregnant,
your nuclear medicine doctor will only administer this medicine during pregnancy if a benefit is expected which would outweigh the risks.

If you are breastfeeding,
please tell your nuclear medicine doctor, as he/she will advise you to stop doing so until the radioactivity has left your body. This takes about 24 hours. The expressed milk should be discarded. Please ask your nuclear medicine doctor when you can resume breast-feeding .

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your nuclear medicine doctor for advice before taking this medicine.

Driving and using machines
It is considered unlikely that X will affect your ability to drive or to use machines.

X contains sodium
<This medicine contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially 'sodium- free'>.

<The administration of this medicine can contain more than 23 mg of sodium. This should be taken into account if you are on low sodium diet. Please ask your nuclear medicine doctor.>

3. How X is used

There are strict laws on the use, handling and disposal of radiopharmaceutical products. X will only be used in special controlled areas. This product will only be handled and given to you by people who are trained and qualified to use it safely. These persons will take special care for the safe use of this product and will keep you informed of their actions.

The nuclear medicine doctor supervising the procedure will decide on the quantity of X to be used in your case. It will be the smallest quantity necessary to get the desired information.
The quantity usually recommended to be administered for an adult ranges depending on the test to be performed, and ranges between 200 and 2000 MBq (Megabecquerel, the unit used to express radioactivity).

Use in children and adolescents
In children and adolescents, the quantity to be administered will be adapted to the child's weight.

Administration of X **and conduct of the procedure**
X is administered in a vein of the arm or the foot (intravenous administration).
One to two injections is sufficient to conduct the test that your doctor needs.
After injection, you will be offered a drink and asked to urinate immediately preceding the test.
The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.
The ready-to-use solution will be injected to you in a vein before the scintigraphy is taken. The scanning may take place within 5 to 10 minutes or up to 6 hours after injection, depending on the test.

In the case of a heart investigation, two injections may be necessary, one at rest and one at stress (e.g., during a physical exercise or pharmacological stress). The two injections will be done at least two hours apart and not more than 2000 MBq in total (1 day protocol) will be administered. A two day protocol is feasible, also.

For the scintigraphy of breast abnormalities, an injection of 750 to 1100 MBq is administered into a vein of your arm opposite to the breast concerned, or into a vein of your foot.

To find the position of overactive parathyroid glands, the activity administered is between 185 and 1100 MBq, depending on the methods used.

If the medicine is going to be used to perform images of your heart, then you will be asked not to eat anything for at least 4 hours before the test. After the injection, but before the image (scintigraphy) is made, you will be asked to eat a light fatty meal, if possible, or to drink one or two glasses of milk in order to decrease the radioactivity in your liver and to improve the image.

Duration of the procedure
Your nuclear medicine doctor will inform you about the usual duration of the procedure.

After administration of X has been performed, you should:
- avoid any close contact with young children and pregnant women for the 24 hours following the injection,
- urinate frequently in order to eliminate the product from your body.

The nuclear medicine doctor will inform you if you need to take any special precautions after receiving this medicine. Contact your nuclear medicine doctor if you have any questions.

If you have been given more X than you should
An overdose is almost impossible because you will only receive a dose of X precisely controlled by the nuclear medicine doctor supervising the procedure. However, in the case of an overdose, you will receive the appropriate treatment. In particular, the nuclear medicine doctor in charge of the procedure may recommend that you drink abundantly in order to facilitate the elimination of X from your body.

Should you have any further questions on the use of this medicine, please ask the nuclear medicine doctor who supervises the procedure.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Allergic reactions possibly with shortness of breath, extreme tiredness, being sick (usually within 2 hours after administration), swelling beneath the skin that can occur in areas such as the face and limbs (angioedema), and obstruct the airway, or leading to a dangerous decrease of blood pressure (hypotension) and slow heart beat (bradycardia) have been seen rarely. Doctors are aware of this possibility and have emergency treatment available for use in such cases. Local skin reactions have also been seen rarely with itching, hives, rash, swelling and redness. If you experience any of those, please refer immediately to your nuclear medicine doctor.

Other possible side effects are listed in the order of their frequency below:

Frequency	Possible side effects
common: may affect up to 1 in 10 people	Metallic or bitter taste, smell alteration, and dry mouth immediately after injection.
uncommon: may affect up to 1 in 100 people	Headache, chest pain, abnormal ECG and feeling sick.
rare: may affect up to 1 in 1,000 people	abnormal heart rhythm, local reactions at the injection site, stomach ache, fever, fainting, seizures, dizziness, flushing, skin numbness or tingling, tiredness, joint pains and stomach upset (dyspepsia).
not known: frequency cannot be estimated from the available data	Erythema multiforme, a widespread rash of skin and mucosa.

This radiopharmaceutical will deliver low amounts of ionising radiation associated with the least risk of cancer and hereditary abnormalities.

Reporting of side effects
If you get any side effects, talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in

Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How X is stored

You will not have to store this medicine. This medicine is stored under the responsibility of the specialist in appropriate premises. Storage of radiopharmaceuticals will be in accordance with national regulation on radioactive materials.

The following information is intended for the specialist only.

This medicine must not be used after the expiry date which is stated on the <label> <carton> <bottle> <...> <after {abbreviation used for expiry date}.> <The expiry date refers to the last day of that month.>

<This medicine will not be used if it is noticed {description of the visible signs of deterioration}.>

6. Contents of the pack and other information

What X contains

- The active substance is [tetrakis(1-isocyanide-2-methoxy-2-methylpropy)copper(I)] tetrafluoroborate.
  One vial contains [...] mg [tetrakis(1-isocyanide-2-methoxy-2-methylpropy)copper(I)] tetrafluoroborate.
- The other ingredients are *[Product specific]*.

What X looks like and contents of the pack
The product is a kit for radiopharmaceutical preparation.

X consists of *[product specific]* which has to be dissolved in a solution and combined with radioactive technetium before use as an injection. Once the radioactive substance sodium pertechnetate (^{99m}Tc) is added to the vial, technetium (^{99m}Tc) sestamibi is formed. This solution is ready for injection.

Pack size
[Product specific]

Marketing Authorisation Holder and Manufacturer
{Name and address}
<{tel}>
<{fax}>
<{e-mail}>

This leaflet was last revised in {MM/YYYY} {month YYYY}

<Other sources of information>

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu

<This leaflet is available in all EU/EEA languages on the European Medicines Agency website.>

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The following information is intended for healthcare professionals only:

The complete SmPC of X is provided <as a separate document> <as a tear-off section at the end of the printed leaflet> in the product package, with the objective to provide healthcare professionals with other additional scientific and practical information about the administration and use of this radiopharmaceutical.

Please refer to the SmPC [SmPC should be included in the box].