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SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Guideline on core SmPC and package leaflet for technetium (^{99m}Tc) macrosalb

Draft

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Comments should be provided using this template. The completed comments form should be sent to radiopharmaceuticalsdg@ema.europa.eu

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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 (^{99m}Tc) macrosalb.

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 SmPC for technetium (^{99m}Tc) macrosalb. This guideline should be read in conjunction with the core SmPC and Package Leaflet for Radiopharmaceuticals[1], the QRD product information templates and the guideline on Summary of Product Characteristics.

This core SmPC has been prepared on the basis of national SmPCs, and taking into account the published scientific literature. Any marketing authorisation application or variation of a marketing authorisation for a radiopharmaceutical product containing technetium (^{99m}Tc) macrosalb should be accompanied by the required data and documents for the application to be valid.

The indications in section 4.1 of this core SmPC are provided as possible clinical settings at the time of publication of this core SmPC. However, this list of clinical settings does not waive the need to submit the required studies to support the claimed indication or an extension of indication.

2. Scope

This core SmPC and Package Leaflet covers technetium (^{99m}Tc) macrosalb.

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) macrosalb

[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)

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 kit for radiopharmaceutical preparation}

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains [...] mg macrosalb.

The particles number per vial is [...] x 10^6 ± […]%. In the labelled product the particle size distribution is as follows: more than [...] % of the particles are between 10 and 100 micrometer. To guarantee the right amount of particles after radiolabelling, see section 12.

{(Invented) name} is prepared from human serum albumin derived from human blood donations tested according to the EU Regulations.

The radionuclide is not part of the kit.

Excipient(s) with known effect
[Product specific]

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.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the product obtained is indicated in adults and paediatric population for:

Pulmonary perfusion scintigraphy

For the diagnosis or exclusion of pulmonary embolism in patients with symptoms of pulmonary embolism and for monitoring the evolution of a pulmonary embolism;

For examinations concomitant to therapies that result in a significant reduction in the regional lung perfusion, as preoperative investigation of local pulmonary perfusion prior to (partial) lung resection, preoperative examination and progress monitoring of lung transplants and for pre-therapeutic examinations for assisting radiation therapy planning.

In combination with ventilation scintigraphy for the initial evaluation and the follow-up of patients with severe obstructive and/or restrictive pulmonary diseases.

For the diagnosis and quantification of pulmonary right-to-left shunts.

Radionuclide venography

As an alternative to Doppler ultrasound, for radionuclide venography of the lower limbs, in combination with pulmonary perfusion scintigraphy in patients with both suspected lower limb deep vein thrombosis and pulmonary embolism.

4.2 Posology and method of administration

This medicinal product must be administered exclusively by authorised personnel (see section "General warnings" in section 4.4).

Posology

Adult and elderly patients

The recommended radioactivity intravenously administered is between 40 and 150 MBq, with a middle value of 100 MBq for planar pulmonary perfusion scintigraphy and up to 200 MBq for SPECT pulmonary perfusion scintigraphy. The average recommended number of particles for adults should fall within the range of 100,000 and 300,000. The maximum number of particles of 700,000 per administration must not be exceeded. The minimum number of particles per dosage administered should be 100,000 in order to obtain optimal image quality.

For Adult and elderly patients with severe cardiovascular disease, with pulmonary hypertension accompanied by respiratory insufficiency or with a right-to-left shunt, the number of particles should be reduced between 100,000 and 200,000.

Renal impairment/Hepatic impairment

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

Paediatric population

The Paediatric Task Group of the EANM recommends calculation of the activity administered to the paediatric population on the basis of body weight in accordance with table 1.

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 5.6 MBq. The minimum activity is 10 MBq.

Table 1: Weight-dependent correction factors in the paediatric population according to the EANM-May 2008 guidelines

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

The number of particles should be kept as low as possible in order to embolise no more than 0.1% of the total lung capillary vessels. The number of particles to be administered to children and adolescents is recommended to be calculated according the recommendations of the European Association of Nuclear Medicine (EANM) guidelines for lung scintigraphy in children (2007):

Weight [kg]	**Maximum number of particles to be administered**
<10 Kg	10,000-50,000
10-20 Kg	50,000-150,000
20-35 Kg	150,000-300,000
35-50 Kg	300,000-500,000

In case of known or suspected severe decrease of the pulmonary vascular bed (more then 50%), the number of particles to be administered should be proportionally reduced.
For evaluation of right to left shunts, the number of administered particles should be reduced to 10,000-20,000.

Method of administration
For <multidose> <single use>.

This medicinal product should be reconstituted before administration to the patient.
For instructions on reconstitution of the medicinal product before administration, see section 12.
After radiolabelling the technetium (^{99m}Tc) macrosalb product is a white liquid suspension of particles which may separate on standing.

The contents of the syringe must be carefully swirled once again prior to the injection, in order to achieve a uniform distribution of the particles and in order to avoid the formation of larger-sized aggregates. A thin cannula should be used in order to disperse any complexes of aggregates present.
For the same reason, blood should never be drawn up into the syringe because that induces the formation of small clots, which are presented in the scintigraphy as false positive defects because of the occlusion of the bigger arterioles. If possible, the product should not be injected via an implanted venous access device, as this can result in inadequate mixing of the radioactivity in the pulmonary artery.
The content of the vial should be used only for the preparation of the injectable suspension of human albumin macroaggregates labelled with technetium-99m. Direct administration to patients before completing the procedure must be avoided.
After the patient has coughed and taken several deep breaths, the medicinal product is slowly injected intravenously over 3 to 5 respiratory cycles or for at least 30 seconds, if possible however, not via an implanted venous catheter. Great care must be taken to see that the radioactive product does not enter the surrounding tissues and that no blood is aspirated, as otherwise there is a danger that larger complexes of aggregates will form. The patient should lie on his back during the injection or as close to this position as possible for patients with orthopnea. The pulmonary investigation can begin immediately after the injection.
The intravenous injection is carried out on official recommendation in the supine position, the craniocaudal difference being thus evened out. On the other hand there are sources that advise carrying out

the injection in the same position in which inhalation of the radioactive inert gas or of aerosols is undertaken, i.e. preferably in the sitting position, this position being taken up at least 5 minutes beforehand. In this way, as a consequence of the better ventilation of the lungs in the sitting position, the danger of false positive results in a staggered investigation of ventilation and perfusion is avoided.

For patient preparation, see section 4.4.

Image acquisition
The pulmonary imaging can start immediately after injection.

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 product.

Severe pulmonary hypertension.

4.4 Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions

The possibility of hypersensitivity, including serious life-threatening or fatal anaphylactic/anaphylactoid reactions, should always be considered.
If hypersensitivity or anaphylactic reactions occur, the administration of the medicinal product must be discontinued immediately and intravenous treatment initiated, if necessary. To enable immediate action in emergencies, the necessary medicinal products and equipment such as endotracheal tube and ventilator must be immediately available.

Individual benefit/risk justification

For each patient, the radiation exposure must be justifiable by the likely benefit. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Careful caution should be taken when administering technetium (^{99m}Tc) macrosalb to patients with pulmonary hypertension, respiratory insufficiency, possible or known right-to-left cardiac shunt or pulmonary transplant patients. In these cases, technetium (^{99m}Tc) macrosalb may not be administered except after a careful benefit/risk analysis.

In order to minimise the possibility of microembolism to the cerebral and renal circulations, technetium (^{99m}Tc) macrosalb product should be administered by slow intravenous injection. The particles number must be kept as low as possible. In adults the particles number can be reduced to between 100,000 and 200,000 particles without loss of image quality for detection of perfusion defects without affecting the quality of images for the visualization of perfusion defects. Heterogeneous distribution of the radioactivity may occur when the number of particles is below 100.000 units.

Renal impairment/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 sections 4.2. and 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.
A thyroid blockade prior to application of the technetium (^{99m}Tc) macrosalb injection suspension can help to reduce the radiation exposure of the thyroid by reducing the thyroid-uptake of technetium (^{99m}Tc) pertechnetate which develops in lesser amounts by the metabolism.

After the procedure

Close contact with infants and pregnant women should be restricted during the initial 12 hours following the injection.

Specific warnings

[*Product specific*]

It is strongly recommended that every time that {name of product} is administered to a patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection, and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded.

This also applies to unknown or emerging viruses and other pathogens.

There are no reports of virus transmissions with albumin manufactured according to European Pharmacopoeia specifications by established processes.

<This medicinal product contains less than 1 mmol sodium (23 mg) per dose, 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 patients on a 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

Changes in the biological distribution of technetium (^{99m}Tc) macrosalb may be induced by different medicinal products.

- Pharmacologic interactions may be caused by chemotherapeutic medicinal products, heparin and bronchodilators.
- Toxicological interactions may be caused by heroin, nitrofurantoin, busulfan, cyclophosphamide, bleomycin, methotrexate, methysergide.
- Pharmaceutical interactions may be caused by magnesium sulphate. Complexes of most voluminous aggregates can form after treatment with albumin macroaggregates labelled with technetium-99m in patients receiving intravenous therapy with magnesium sulphate; these may pass into the pulmonary circulation.

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 the foetus.

Breast-feeding

Before administering radiopharmaceuticals to a mother who is breast-feeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breast-feeding, and to what is the most appropriate choice of radiopharmaceuticals, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for 12 hours and the expressed feeds discarded.

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

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 2.2 mSv, when the maximal recommended activity of 200 MBq is administered these adverse reactions are expected to occur with a low probability.

The frequencies of undesirable effects are defined as follows:
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) and not known (cannot be estimated from the available data).

Immune system disorders

Frequency not known: Hypersensitivity reactions such as urticaria, shivering fits, fever, nausea, reddening of the face and sweating as well as impairments of cardiac and circulatory functions in the form of changes in respiration, pulse, blood pressure and collapse which may be related to vascular occlusion.
Very rare: Serious anaphylactoid reactions including shock with possible fatal outcome have been reported. The appearance of these reactions may also not be immediate.

General disorders and administration site conditions

Frequency not known: Local allergic reactions at the injection site have been observed

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

The number of macrosalb particles per adult patient must not exceed 1.5×10^6.

An administration of a very high number of particles can lead to a hemodynamically significant vascular blockage. When pronounced changes in respiration, pulse and blood pressure occur, respiratory and circulatory stabilising measures should be taken.

In the event of administration of a radiation overdose the absorbed dose with technetium (^{99m}Tc) macrosalb to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by frequent micturition or by forced diuresis and frequent bladder voiding. <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), particles for injection, ATC code: V09EB01.

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

5.2 Pharmacokinetic properties

Distribution

Following intravenous injection of technetium (^{99m}Tc) macrosalb, temporary occlusion of pulmonary capillaries and arterioles occurs, which is proportional to the regional pulmonary blood flow at the time.

Organ uptake

The principle of perfusion scintigraphy is capillary blockade. The albumin macroaggregate particles do not penetrate the lung parenchyma (interstitial or alveolar) but remain in a temporary occlusive position in the lumen of the capillary. After intravenous injection most of the macrosalb aggregates are retained in the arterioles and capillaries of the lung at the time of first passage through the lungs. The diameter of most of the macroaggregates is between 10 and {x} micrometer. Depending on the distribution of particle sizes, roughly every 1,000,000th capillary (diameter < 20 micrometer) and every 1,000th arteriole (diameter > 20 micrometer) is temporarily occluded. The extent of the regional blockade with micro embolisms is thus directly proportional to the regional lung perfusion at the time. Larger particles can lead to occlusion of larger vessels and therefore cause artificial perfusion disturbances. Hemodynamic changes are directly linked to the particle size of the macrosalb aggregates.

Elimination

The elimination of the macroaggregate particles from the lungs takes place by mechanical fragmentation through the systolic-diastolic pressure pulses within the capillaries and by enzymatic breakdown with subsequent phagocytosis by macrophages of the reticuloendothelial system. In the context of elimination, activity accumulates in the liver and kidneys.

Liver accumulation is extremely variable; it increases over time and can become as high as approximately 25%. With regard to elimination from the lungs, great differences exist between individuals. The particles are eliminated from the lungs with a biological half-life of about 7-20 hours. 30-45% of the injected radioactivity is excreted through the urine within 24 hours.

If a right-to-left shunt is present, a proportion of the macroaggregates moves into the general circulation system and becomes trapped there in the capillary bed. If this happens, the formation of a cerebral or renal microembolism is, for example, possible.

Half-life

[State biological half-life and effective half-life (including biological and physical half-lives)]

<Renal/Hepatic impairment>

<The pharmacokinetics in patients with renal or hepatic impairment has not been characterised.>

5.3 Preclinical safety data

Correlation exists between the size of the particles and their toxic effects.

The pathophysiologic mechanism responsible for toxicity is shown to be the increase of the pulmonary blood pressure. With particulars from 10 to 50 micrometer in diameter the first pulmonary signs of toxicity in dogs (*e.g.* tachypnea) appear after injection of 20 to 25 mg per kg of body weight.

A sharp increase of the pulmonary blood pressure is noticed when 20 mg of less than 80 micrometer sized macrosalb particles are injected, where no significant pressure changes are recorded with 40 mg of less than 35 micrometer macrosalb particles.

With suspension of macrosalb particles up to 150 micrometer diameter, no blood pressure changes appear below 10 mg/kg, while larger diameter suspensions (up to 300 micrometer) typical blood pressure changes in pulmonary artery appear when the doses exceed 5 mg/kg.

Doses of 20-50 mg/kg cause sudden death from failure. A safety factor of 100 is found after injection in dogs of 14,000 particles of technetium (^{99m}Tc) macrosalb (size: 30 -50 micrometer).

The repeated-dose toxicity studies performed in dogs show no detectable variations in the general behaviour of the animals.

No evidence of pathological changes in the main organs has been detected.

There is no evidence in the literature of teratogenic, mutagenic or carcinogenic effect of the unlabelled product.

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 6.6 and 12.
The medicinal product should not come into contact with air.

6.3 Shelf life

[Product specific]
Kit in the original pack: [product specific]
After radiolabelling: [...] hours. Do not store above [...]°C after radiolabelling.

6.4 Special precautions for storage

[Product specific].
< Keep the vials in the outer carton in order to protect from light.>

For storage conditions after reconstitution and 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]
<Single> <Multidose> vial.
<Not all pack sizes may be marketed>

6.6 Special precautions for disposal <and other handling>

General warning

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

Radiopharmaceuticals should be prepared 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) macrosalb 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.

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) solution 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 etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Any unused suspension should be discarded 12 hours after radiolabelling. Any unused 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 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 which, in view of its long half-life of 2.13 x 10^5 years can be regarded as quasi stable.

The data listed below are from ICRP 80 publication.

Organ	Absorbed dose per unit activity administered (mGy/MBq)				
	Adults	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0068	0.0088	0.013	0.019	0.031
Bladder	0.0087	0.011	0.014	0.016	0.030
Bone surfaces	0.0051	0.0064	0.0091	0.014	0.026
Brain	0.00092	0.0012	0.0020	0.0032	0.0055
Breasts	0.0050	0.0056	0.0099	0.014	0.021
Gall bladder	0.0056	0.0070	0.010	0.016	0.024
Gastrointestinal tract					
Stomach	0.0037	0.0052	0.0080	0.012	0.020
Small intestine	0.0020	0.0026	0.0043	0.0068	0.012
Colon	0.0019	0.0026	0.0043	0.0069	0.012
(Upper large intestine	0.0022	0.0029	0.0050	0.0083	0.014)
(Lower large intestine	0.0016	0.0021	0.0033	0.0050	0.0095)
Heart	0.0096	0.013	0.018	0.025	0.038
Kidneys	0.0037	0.0048	0.0072	0.011	0.018
Liver	0.016	0.021	0.030	0.042	0.074
Lungs	0.066	0.097	0.13	0.20	0.39
Muscles	0.0028	0.0037	0.0052	0.0077	0.014
Oesophagus	0.0061	0.0077	0.011	0.015	0.022
Ovaries	0.0018	0.0023	0.0035	0.0054	0.010
Pancreas	0.0056	0.0075	0.011	0.017	0.029
Red marrow	0.0032	0.0038	0.0053	0.0072	0.012
Skin	0.0015	0.0017	0.0027	0.0043	0.0078
Spleen	0.0041	0.0055	0.0083	0.013	0.022
Testes	0.0011	0.0014	0.0022	0.0033	0.0062
Thymus	0.0061	0.0077	0.011	0.015	0.022
Thyroid	0.0025	0.0033	0.0057	0.0090	0.016
Uterus	0.0022	0.0028	0.0042	0.0060	0.011
Remaining organs	0.0028	0.0036	0.0050	0.0074	0.013
Effective dose (mSv/MBq)	**0.011**	**0.016**	**0.023**	**0.034**	**0.063**

The effective dose resulting from the administration of a (maximal recommended) activity of 150 MBq for planar perfusion scintigraphy for an adult weighing 70 kg is about 1.7 mSv and 2.2 mSv for 200 MBq (maximum recommended dose for SPECT).

For an administered activity of 150 MBq the typical radiation dose to the target organ (the lungs) is 10 mGy and the typical radiation dose/doses to the critical organ/organs *(*adrenal glands, bladder wall, liver, pancreas and spleen) are 1.0, 1.3, 2.4, 0.8 and 0.6 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.

Estimation of volume and activity of Sodium Pertechnetate (^{99m}Tc) in relation with the number of macrosalb particles and activity per dose

[*Product specific*]

For consistency with section 4.2. "Posology and method of administration" it is necessary to define the volume and radioactivity of the Sodium Pertechnetate (^{99m}Tc) solution to be added to the kit in relation to the activity and to the number of particles of macroaggregates to be administered to adults or pediatric patients.

The following procedure and formulations should be considered on this purpose.

1. The first step consists in the determination of the labelling volume of the macroaggregate, to be injected per dose.

The calculation formula is the following:

$$\text{Labelling volume} = \frac{\text{Number of macroaggregate particles per vial } (2\text{x}10^6) \times \text{Volume to inject}}{\text{Number of macroaggregate particles to be injected per dose}}$$

2. The second step consists in the determination of the total activity to add to the vial as a function of the activity to be injected and the volume of the eluate.

The calculation formula is the following:

$$\text{Radioactivity for the labelling} = \frac{\text{Activity to be injected} \times \text{Labelling volume}}{\text{Volume to be injected}}$$

The two tables below show examples for adult and pediatric patients.

Radioactive values also take into account the radioactive decay of the Technetium-99m.

Calculation refers to a mean of 2 x 10^6 of macroaggregate particles per vial.

Adults

Labelling volume (ml)	**Total labelling activity (MBq) at T_0**	**Volume to be injected (ml)**	**N. macroaggregate particles /dose**	**Activity/dose depending on decay of the Technetium-99m**
{x}	{x}	{x}	{x}	{x} MBq (T_0)
				{x} MBq (T_0 + x h)

Pediatric patient

weight (kg)	**Activity/ dose (MBq)**	**Volume to be injected (ml) at T_0**	**Volume to be injected (ml) at T= 3 from the labelling**	**Volume to be injected (ml) at T= 4 from the labelling**	**N. macroaggregate particles/dose**
{x}	{x}	{x}	{x	{x}	{x}

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>

PACKAGE LEAFLET

Package Leaflet: Information for the patient

{(Invented) name strength kit for radiopharmaceutical preparation}

macrosalb

<▼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 should be radiolabelled with 'technetium-99m' and obtained product is used for scintigraphic imaging in adults and children.

When it is injected, the product is temporarily taken up by certain organs. Since the product contains a small amount of radioactivity, it can be visualised from outside the body using special cameras, and an image can be taken (known as a scan). This scan shows the distribution of the radioactivity in the organ and how that organ is functioning.

X can be used for lung scans. These scans provide information about the structure of the lungs and the blood flow through the lung tissue.

X can also be used to show how the blood flows through the veins.

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 human serum albumin or any of the other ingredients of this medicine (listed in section 6).
- if you have severe pulmonary hypertension (unusually high blood pressure in the arteries of the lungs). In case of doubt, it is important to consult your doctor.

Warnings and precautions

You should inform your nuclear medicine doctor:

- if you have unusually high blood pressure in the arteries of the lungs (severe pulmonary hypertension), respiratory insufficiency or if you are aware of having a cardiac anomaly known as a cardiac right-to-left shunt.
- if you are pregnant or believe you may be pregnant.
- if you are breastfeeding.
- if you suffer from kidney or liver disease.
- if you use heroin.

Your nuclear medicine doctor will inform you if you need to take any special precautions in those cases.
Talk to your nuclear medicine doctor if you have any questions.

Before administration of X you should

- 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 or your child is under 18 years old.

Medicines made from human blood or plasma

When medicines are made from human blood or plasma, certain measures are put in place to prevent infections being passed on to patients. These include:

- careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded,
- the testing of each donation and pools of plasma for signs of virus/infections,
- the inclusion of steps in the processing of the blood or plasma that can inactivate or remove viruses.

Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses or other types of infections.
There are no reports of virus infections with albumin manufactured to European Pharmacopoeia requirements by established processes.

Other medicines and X

Tell your nuclear medicine doctor if you are <taking><using>, have recently <taken><used> or might <take><use> any other medicines since they may interfere with the interpretation of the images.

Please ask your nuclear medicine doctor before taking any medicines.
Specific examples include:

- a medicine to prevent blood clotting (heparin)
- cancer medicines (busulfan, cyclophosphamide, bleomycin, methotrexate)
- medicines used to treat asthma and chronic obstructive pulmonary disease (bronchodilators)
- some antibiotics (for example nitrofurantoin)
- some medicines used in the prevention of headache (for example methysergide)
- a medicine used for substitution of electrolytes (magnesium sulphate)

Pregnancy and 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 you are given this medicine.

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:

The nuclear medicine doctor will only administer X during pregnancy if a benefit is expected which would outweigh the risks.

If you are breast-feeding:

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 12 hours. The expressed milk should be discarded.

Please ask your nuclear medicine doctor when you can resume breastfeeding.

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'>.

<Your dose of this medicine may 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 require getting the desired information. The quantity to be administered usually recommended for an adult ranges from 40 to 200 MBq (megabecquerel, the unit used to express radioactivity).

Use in children and adolescents

In children and adolescents under 18 years, the quantity to be administered will be adapted to the child's weight.

Administration of X and conduct of the procedure

X is administered by injection in a vein. This product is not intended for regular or continuous administration.

One injection is sufficient to conduct the test that your doctor needs. The tests can be carried out any time after you have received the injection. Precisely when the test will be carried out depends on the type of examination.

After injection, you will be offered a drink and asked to urinate immediately preceding the test.

Duration of the procedure

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

After administration of X, you should:

- avoid any close contact with young children and pregnant women for the initial 12 hours following the administration.
- drink as much as possible the day after treatment. This will help the traces of radioactivity leave your body more quickly.
- 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 impossible because you will only receive a single dose of X precisely controlled by the nuclear medicine doctor supervising the procedure. However, an administration of a very high number of particles can lead to a vascular blockage. Take care if pronounced changes in respiration, pulse or blood pressure occur; in this case your nuclear medicine doctor will take adequate measures.

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 question on the use of X, 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.

*Frequency not known (*cannot be estimated from the available data)

Allergic reactions (Frequency not known): Urticaria (hives), shivering fits, fever, nausea, reddening of the face and sweating as well as impairments of cardiac and circulatory functions in the form of changes in respiration, pulse, blood pressure and collapse. Local allergic reactions in the form of redness, swelling, and itching at the injection site have been observed. In such case you should contact your nuclear medicine doctor.

Very rare: (*Less than 1 patient out of 10000)*

Serious allergic reactions (: Serious allergic reactions including shock with possible fatal outcome have been reported. The appearance of these reactions may also not be immediate.

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

If you get any side effects talk to your nuclear medicine doctor. This includes any possible side effects not listed in this leaflet.

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. 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 to store X

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.

X 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.>

<X 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 macrosalb which is macroaggregates from human serum albumin, a natural protein from human blood
- One vial contains [..] mg macroaggregates of human serum albumin.
- The other ingredients are [*product specific*]

What X looks like and contents of the pack

The product is a kit for radiopharmaceutical preparation.

<Each vial contains white or almost white lyophilisate for preparation of an injection suspension>.

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) macrosalb is formed. This solution is ready for injection.

Pack size

[*Product specific*]

Marketing Authorisation Holder and Manufacturer

{Name and address}

<{tel}>

<{fax}>

<{e-mail}>

<For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
{Nom/Naam/Name}
<{Adresse/Adres/Anschrift }
B-0000 {Localité/Stad/Stadt}>
Tél/Tel: + {N° de téléphone/Telefoonnummer/ Telefonnummer}
<{e-mail}>

Lietuva
{pavadinimas}
<{adresas}
LT {pašto indeksas} {miestas}>
Tel: +370{telefono numeris}
<{e-mail}>

България
{Име}
<{Адрес}
{Град} {Пощенски код}>
Тел.: + {Телефонен номер}

Luxembourg/Luxemburg
{Nom}
<{Adresse}
L-0000 {Localité/Stadt}>
Tél/Tel: + {N° de téléphone/Telefonnummer}

<{e-mail}>

Česká republika
{Název}
<{Adresa}
CZ {město}>
Tel: +{telefonní číslo}
<{e-mail}>

Danmark
{Navn}
<{Adresse}
DK-0000 {by}>
Tlf: + {Telefonnummer}
<{e-mail}>

Deutschland
{Name}
<{Anschrift}
D-00000 {Stadt}>
Tel: + {Telefonnummer}
<{e-mail}>

Eesti
(Nimi)
<(Aadress)
EE - (Postiindeks) (Linn)>
Tel: +(Telefoninumber)
<{e-mail}>

Ελλάδα
{Όνομα}
<{Διεύθυνση}
GR-000 00 {πόλη}>
Τηλ: + {Αριθμός τηλεφώνου}
<{e-mail}>

España
{Nombre}
<{Dirección}
E-00000 {Ciudad}>
Tel: + {Teléfono}
<{e-mail}>

France
{Nom}
<{Adresse}
F-00000 {Localité}>
Tél: + {Numéro de téléphone}
<{e-mail}>

Hrvatska
{Ime}
<{e-mail}>

Magyarország
{Név}
<{Cím}
H-0000 {Város}>
Tel.: +Telefonszám}
<{e-mail}>

Malta
{Isem}
<{Indirizz}
MT-0000 {Belt/Raħal}>
Tel: + {Numru tat-telefon}
<{e-mail}>

Nederland
{Naam}
<{Adres}
NL-0000 XX {stad}>
Tel: + {Telefoonnummer}
<{e-mail}>

Norge
{Navn}
<{Adresse}
N-0000 {poststed}>
Tlf: + {Telefonnummer}
<{e-mail}>

Österreich
{Name}
<{Anschrift}
A-0000 {Stadt}>
Tel: + {Telefonnummer}
<{e-mail}>

Polska
{Nazwa/ Nazwisko:}
<{Adres:}
PL – 00 000{Miasto:}>
Tel.: + {Numer telefonu:}
<{e-mail}>

Portugal
{Nome}
<{Morada}
P-0000–000 {Cidade}>
Tel: + {Número de telefone}
<{e-mail}>

România
{Nume}

<{Adresa}
{Poštanski broj} {grad}>
Tel: + {Telefonski broj}
<{e-mail}>

Ireland
{Name}
<{Address}
IRL - {Town} {Code for Dublin}>
Tel: + {Telephone number}
<{e-mail}>

Ísland
{Nafn}
<{Heimilisfang}
IS-000 {Borg/Bær}>
Sími: + {Símanúmer}
<{Netfang }>

Italia
{Nome}
<{Indirizzo}
I-00000 {Località}>
Tel: + {Numero di telefono}>
<{e-mail}>

Κύπρος
{Όνομα}
<{Διεύθυνση}
CY-000 00 {πόλη}>
Τηλ: + {Αριθμός τηλεφώνου}
<{e-mail}>

Latvija
{Nosaukums}
<{Adrese}
{Pilsēta}, LV{pasta indekss }>
Tel: + {telefona numurs}
<{e-mail}>

<{Adresă}
{Oraş} {Cod poştal} – RO>
Tel: + {Număr de telefon}
<{e-mail}>

Slovenija
{Ime}
<{Naslov}
SI-0000 {Mesto}>
Tel: + {telefonska številka}
<{e-mail}>

Slovenská republika
{Názov}
<{Adresa}
SK-000 00 {Mesto}>
Tel: + {Telefónne číslo}
<{e-mail}>

Suomi/Finland
{Nimi/Namn}
<{Osoite/Adress}
FIN-00000 {Postitoimipaikka/Stad}>
Puh/Tel: + {Puhelinnumero/Telefonnummer}
<{e-mail}>

Sverige
{Namn}
<{Adress}
S-000 00 {Stad}>
Tel: + {Telefonnummer}
<{e-mail}>

United Kingdom
{Name}
<{Address}
{Town} {Postal code} – UK>
Tel: + {Telephone number}
<{e-mail}>>

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

<This medicine has been given 'conditional approval'. This means that there is more evidence to come about this medicine.
The European Medicines Agency will review new information on this medicine at least every year and this leaflet will be updated as necessary.>

<This medicine has been authorised under 'exceptional circumstances'. This means that <because of the rarity of this disease> <for scientific reasons> <for ethical reasons> it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.>

<Other sources of information>

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu<, and on the website of {name of MS Agency (link)}>. <There are also links to other websites about rare diseases and treatments.>

<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 {(Invented) name} is provided as <a separate document> <as a tear-off section at the end of 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 included in the box.