



213620

ENGLISH

DRAX IMAGE®

Macrosalb DRAXIMAGE 2.5 mg Lyophilisate for suspension for injection / kit for radiopharmaceutical preparation

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Macrosalb DRAXIMAGE 2.5 mg lyophilisate for suspension for injection / kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 2.5 mg macrosalb (macroaggregated human albumin). The radioisotope is not part of the kit.

In the labelled product, the particle size distribution (largest dimension) is as follows: more than 90% of the particles are between 10 and 70 µm and less than 10% are smaller than 10 µm. None of the particles are larger than 150 µm. The number of particles per vial is between 4×10^6 and 8×10^6 . To guarantee the right amount of particles after radiolabelling, see section 12.

Excipients:

Each vial also contains approximately 0.23 mg (0.01 mmol) of sodium.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Lyophilisate for suspension for injection.

Kit for radiopharmaceutical preparation.

The product is a white freeze-dried plug that may break into powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

Macrosalb DRAXIMAGE is used after labelling with a sodium pertechnetate [^{99m}Tc] solution (Ph. Eur.) obtained from an authorised radionuclide generator in the following indications:

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 of regional lung perfusion, as preoperative investigation of local pulmonary perfusion prior to (partial) pulmonary resection, for 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

Dosage instructions for Pulmonary Perfusion Scintigraphy and Venoscintigraphy

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 between 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.

Adult and elderly patients with severe cardiovascular disease, with pulmonary hypertension accompanied by respiratory insufficiency or with right-to-left shunt.

The number of particles is to be reduced between 100,000 and 200,000.

Paediatric patients

The Pediatric Task Group of the EANM recommends calculation of the activity administered to children on the basis of body weight in accordance with the following Table:

Fraction of the adult dosage:

3 kg = 0,10	22 kg = 0,50	42 kg = 0,78
4 kg = 0,14	24 kg = 0,53	44 kg = 0,80
6 kg = 0,19	26 kg = 0,56	46 kg = 0,82
8 kg = 0,23	28 kg = 0,58	48 kg = 0,85
10 kg = 0,27	30 kg = 0,62	50 kg = 0,88
12 kg = 0,32	32 kg = 0,65	52-54 kg = 0,90
14 kg = 0,36	34 kg = 0,68	56-58 kg = 0,92
16 kg = 0,40	36 kg = 0,71	60-62 kg = 0,96
18 kg = 0,44	38 kg = 0,73	64-66 kg = 0,98
20 kg = 0,46	40 kg = 0,76	68 kg = 0,99

To ensure a sufficient image quality in small children, the administered activity should not be below 10 MBq.

Newborns: The number of particles is to be restricted to a maximum of 50,000.

One-year-old children: The number of particles is to be restricted to a maximum of 150,000.

Paediatric patients where a right-to-left shunt is present

Newborns: The number of particles should be limited to 1,000 – 5,000.

One-year-old children: The number of particles should be limited to 5,000 – 15,000.

5-10 year-old children: The number of particles should be limited to 20,000 – 30,000.

15-year-old adolescents: the number of particles should be limited to 20,000 – 70,000.

Method of administration and scintigraphic examination

This medicinal product must be reconstituted before use. Any unused suspension should be discarded 8 hours after reconstitution. Information on the preparation of the reconstituted product is provided in Section 12. After reconstitution and labelling the technetium [^{99m}Tc] macrosalb injection is a white liquid suspension of particles which may separate on standing.

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

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. Additional information on precautions regarding administration of the suspension may be found in section 4.4.

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 scintigram 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.

Patient Preparation

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 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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients
- Severe pulmonary hypertension

4.4 Special warnings and precautions for use

For all patients, the radiation exposure must be justifiable by the expected diagnostic achieved with the lowest possible radiation dose.

For paediatric patients: (aged less than 18 years) particular caution is required when administering technetium [^{99m}Tc] macrosalb aggregates, as the effective dose per MBq is higher than in adults (see section 11. Dosimetry).

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

Particular caution is required when administering technetium [^{99m}Tc] macrosalb aggregates to patients with pulmonary hypertension, respiratory insufficiency, or possible or known cardiac right-to-left shunt. To minimize the danger of microembolism in the cerebral and renal circulation systems, the technetium [^{99m}Tc] macrosalb aggregates should be administered by slow intravenous injection. The number of particles must be kept as low as possible. In adults the number of particles can be reduced to between 100,000 and 200,000 particles without meaning that image quality for the detection of perfusion defects need suffer as a result. Non-homogenous distribution of activity can occur if the number of particles is reduced to less than 100,000 for an adult. If indications exist of the illnesses listed above, then Macrosalb DRAXIMAGE may not be administered except after a careful benefit/risk analysis has been performed.

In order not to restrict the stability of the radioactively labelled medicinal product, technetium [^{99m}Tc] macrosalb aggregates are not permitted to be mixed with other medicinal products or components nor be administered together with them.

The medicinal product should not come into contact with air.

Viral safety

When medicinal products are manufactured from human blood or plasma, certain measures are instituted in order to prevent transmission of infections to the patient. These include careful selection of blood or plasma donors in order to ensure that persons at risk who might possibly be infection carriers are excluded and the testing of each donation and each plasma pool for indications of viruses or infections. The manufacturers of these products include measures in their processing of blood or plasma that can inactivate or remove viruses.

The product is manufactured exclusively from batches of human albumin collected in the United States, all of which have been tested for Hepatitis B Surface Antigen (HBsAg), antibodies against the Human Immunodeficiency Virus (anti-HIV-1/HIV-2; anti-HTLV1/HTLV2), antibodies against the Hepatitis C virus (anti-HCV) and Antigen to Human Immunodeficiency Virus (HIV-1) and been found to be negative.

Despite these measures, the possibility of a transmission of infectious pathogens cannot be excluded with absolute certainty when medicinal products manufactured from blood or plasma are administered. This applies in equal measure to every unknown or newly emerging virus or to other type of infections.

No reports exist of virus infections from albumin that was manufactured by established processes in accordance with the specifications of the European Pharmacopoeia.

It is urgently recommended that the name and batch number of the product be recorded whenever you receive a dosage of Macrosalb DRAXIMAGE in order to document the batches utilized.

Excipients

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially sodium-free.

General warnings and precautionary measures for avoiding environmental hazards

Radiopharmaceuticals should be received, used and administered only by authorized persons in designated clinical settings and receipt, storage, use, transfer and disposal are subject to the regulations and appropriate licenses of the competent authorities.

Radiopharmaceuticals should be prepared by the user in a manner that satisfies both radiation safety and pharmaceutical quality requirements.

Patients who have been treated with radioactive medicinal products represent a risk factor for other personnel because of the external radiation load or because of contamination caused by being splashed by urine, vomit, etc. Precautionary measures in compliance with national radiation protection regulations are therefore to be observed. Contamination caused by radioactivity being secreted by the patient is to be avoided.

4.5 Interaction with other medicinal products and other forms of interaction

Changes in the biological distribution of ^{99m}Tc-macrosalb are induced by different medicinal products.

- Pharmacologic interactions are caused by chemotherapeutic agents, heparin, bronchodilators.
- Toxicologic interactions are caused by heroin, nitrofurantoin, busulfan, cyclophosphamide, bleomycin, methotrexate, methysergide.
- Pharmaceutic interactions are caused by magnesium sulphate.

4.6 Pregnancy and lactation

There is no experience from the use of technetium [^{99m}Tc] macrosalb injection in pregnant women.

Women of childbearing potential

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

Pregnant women

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

Breast-feeding mothers

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

4.7 Effects on ability to drive and use machines

Macrosalb DRAXIMAGE has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Very rarely ($\leq 1/10,000$), after intravenous administration of technetium [^{99m}Tc] macrosalb aggregates, hypersensitivity reactions appear 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.

Serious anaphylactoid reactions including shock with possible fatal outcome have been reported, but are very rare. The appearance of these reactions may also not be immediate. Local allergic reactions at the injection site have been observed.

If symptoms such as redness, itching, sneezing, coughing, sweating or feeling cold, difficulty breathing, nausea, vomiting, edema, urticaria or other sensitivity reactions occur during injection, administration of the medicinal product must be interrupted immediately. Emergency equipment including the medicinal products necessary for treatment must be ready at hand.

Ionized radiation can cause cancer and genetic changes. As most nuclear medicine investigations are carried out with low effective doses of radiation of less than 20 mSv, the probability of these effects occurring should be regarded as being very slight. The effective dose after administration of the maximum recommended activity of this medicinal product is 2.2 mSv.

4.9 Overdose

Overdose, as commonly interpreted (i.e., excessive quantity in weight) is not expected, but overdose may be understood as the administration of a very high number of particles. The number of macrosalb particles per adult patient must not exceed 1.5×10^6 . To guarantee the right amount of particles after radiolabelling, see section 12.

The dangers to be expected relating to the inadvertent administration of excess radioactivity may be reduced by promoting a diuresis and frequent voiding of urine.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals; Technetium [^{99m}Tc], particles for injection.

ENGLISH

DRAX IMAGE®

Macrosalb DRAXIMAGE 2.5 mg Lyophilisate for suspension for injection / kit for radiopharmaceutical preparation

PACKAGE LEAFLET: INFORMATION FOR THE USER

Active substance: Macrosalb (Macroaggregated human albumin)

Read all of this leaflet carefully before you start using this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

- What Macrosalb DRAXIMAGE is and what it is used for
- Before you use Macrosalb DRAXIMAGE
- How to use Macrosalb DRAXIMAGE
- Possible side effects
- How to store Macrosalb DRAXIMAGE
- Further information

1. WHAT MACROSALB DRAXIMAGE IS AND WHAT IT IS USED FOR

This medicine is for diagnostic use only.

Macrosalb DRAXIMAGE is a radiopharmaceutical product used when a diagnosis is made using radioisotopes.

When it is injected, it is temporarily taken up by a 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 the body, giving the doctor information about the shape of the organ and how that organ is functioning.

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

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

Your doctor will tell you which specific investigation Macrosalb DRAXIMAGE will be used for in your case.

2. BEFORE YOU USE MACROSALB DRAXIMAGE

Do not use Macrosalb DRAXIMAGE

If you are allergic (hypersensitive) to Macrosalb (Macroaggregated human albumin) or any of the ingredients of Macrosalb DRAXIMAGE, or 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.

Take special care with Macrosalb DRAXIMAGE

Special care should be exercised when Macrosalb DRAXIMAGE is administered to children and adolescents.

If you suffer or think you suffer from a heart condition or in particular from severe pulmonary hypertension (unusually high blood pressure in the arteries of the lungs), respiratory insufficiency or if you are aware of having a cardiac anomaly known as a cardiac right-to-left shunt, please bring this to your doctor's attention as such a condition may influence the investigation.

During the use of Macrosalb DRAXIMAGE a small amount of radioactivity is administered. The associated risk is very small. Your doctor will only carry out the investigation if he/she is convinced that the anticipated benefit of the investigation outweighs the risks.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Other medicines may influence the results obtained using Macrosalb DRAXIMAGE. Specific examples include:

- chemotherapeutic agents**,
- a medicine that prevents **blood clotting** (heparin),
- medicines used to treat **asthmatic conditions** (bronchodilators),
- some **antibiotics** (for example, nitrofurantoin),
- some medicines used in the prevention of headaches (for example, **methysergide**),
- a medicine used as an electrolyte replenisher (**magnesium sulphate**)

To avoid interactions with other medicines, it is important that you inform your doctor of all medicines you may be using.

Pregnancy and breastfeeding

It is important to tell your doctor whether there is a chance you may be pregnant. The use of radiopharmaceuticals during **pregnancy** should be considered carefully. Your doctor will only administer this product during pregnancy if a benefit is expected which would outweigh the risks.

If you are **breastfeeding**, please tell your doctor, as he/she may advise you to stop doing so until the radioactivity has left your body. This takes about 12 hours. The expressed milk should be discarded.

Driving and using machines

Macrosalb DRAXIMAGE has no or negligible influence on the ability to drive and use machines.

Important information about some of the ingredients of Macrosalb DRAXIMAGE

Macrosalb DRAXIMAGE contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially sodium – free.

3. HOW TO USE MACROSALB DRAXIMAGE

This radioactive medicinal product may only be used in accordance with your doctor's instructions and under his/her supervision. Macrosalb DRAXIMAGE must be reconstituted with a suitable sodium pertechnetate [^{99m}Tc] solution before it can be administered.

Your doctor will decide what quantity of radioactive Macrosalb DRAXIMAGE should be used. This will be the minimum amount required to obtain a clear scan with sufficient information. The amount can vary from 40 to 200 MBq (megabecquerel, the unit used to express radioactivity). In children lower doses are used, depending on their bodyweight.

- Macrosalb DRAXIMAGE is administered by injection in a vein.
- Macrosalb DRAXIMAGE is administered in one go.
- One injection is sufficient.
- The scans can be carried out any time after you have received the injection. Precisely when the scan will be carried out depends on the type of investigation.

Your doctor may advise you to drink a lot to help the traces of radioactivity leave your body more quickly. This is normal when using diagnostic radiopharmaceuticals. Your doctor will also tell you about any other steps you may need to take following the use of this product.

Do not hesitate to consult your doctor if you are not sure.

If you get more Macrosalb DRAXIMAGE than you should

Since Macrosalb DRAXIMAGE is administered under strictly controlled circumstances by a doctor, it is unlikely that you will be given an overdose. Should this happen nonetheless, the doctor will take appropriate measures.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Macrosalb DRAXIMAGE can cause side effects, although not everybody gets them.

A very small number of patients have experienced hypersensitivity reactions, such as 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.

The appearance of these reactions may also not be immediate. In all these cases the reactions were short-lived and could be treated if necessary.

Very serious allergic reactions including shock with possible fatal outcome have been reported, although rarely.

If any of the side effects gets serious or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE MACROSALB DRAXIMAGE

Keep out of the reach and sight of children.

Do not use Macrosalb DRAXIMAGE after the expiry date which is stated on the vial and the box. The expiry date refers to the last day of that month.

Lyophilized product: Store in a refrigerator (2°C – 8°C).

Labelled product: Store below 25°C.

Shelf life after reconstitution: 8 hours

Storage should be in accordance with national regulations for radioactive material.

Do not use Macrosalb DRAXIMAGE if you notice cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

Following reconstitution, unused radiopharmaceutical and vial should be handled as radioactive waste and disposed of in accordance with local requirements.



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6. FURTHER INFORMATION

What Macrosalb DRAXIMAGE contains

The **active substance** is a natural protein from human blood: macrosalb (macroaggregated human albumin).

Each vial contains 2.5 mg macrosalb.

The **other ingredients** are: stannous chloride dihydrate, human albumin and sodium chloride.

What Macrosalb DRAXIMAGE looks like and contents of the pack

Macrosalb DRAXIMAGE, lyophilisate for suspension for injection/kit for radiopharmaceutical preparation is a white freeze-dried plug that may break into powder.

Pack sizes: 5, 10, 30 or 100 vials.

Not all pack sizes may be marketed.

Marketing authorization holder

DRAXIMAGE (UK) Limited

London, England EC4M7B4

Manufacturer

DRAXIS Specialty Pharmaceuticals Inc.

Kirkland, QC, Canada, H9H 4J4

This medicinal product is authorised in the member states of the EEA under the following names:

- Austria**
Macrosalb DRAXIMAGE 2,5 mg Kit für das radioaktive Arzneimittel Technetium Tc-99m Albumin-Macroaggregat – Injektionslösung
- Belgium**
Macrosalb DRAXIMAGE 2,5 mg lyophilisat pour suspension injectable / trousse pour la préparation de produit radiopharmaceutique
- France**
Macrosalb DRAXIMAGE 2,5 mg lyophilisat pour suspension injectable / trousse pour la préparation de produit radiopharmaceutique
- Germany**
Macrosalb DRAXIMAGE 2,5 mg Lyophilisat zur Herstellung einer Injektionssuspension und Kit für ein radioaktives Arzneimittel.
- Luxembourg**
Macrosalb DRAXIMAGE 2,5 mg lyophilisat pour suspension injectable / trousse pour la préparation de produit radiopharmaceutique
- Netherlands**
Macrosalb DRAXIMAGE 2,5 mg lyofilisaat voor suspensie voor injectie / kit voor radiofarmaceutische bereiding
- Spain**
Macrosalb DRAXIMAGE 2,5 liofilizado para la inyección de suspensión / kit para la preparación radiofarmacéutica
- United Kingdom**
Macrosalb DRAXIMAGE 2.5 mg lyophilisate for suspension for injection / kit for radiopharmaceutical preparation

This leaflet was last approved in 10/2007

ATC code: V09EB01

When administered in usual doses, Macrosalb DRAXIMAGE shows no pharmacodynamic effects detectable clinically or/and analytically.

5.2 Pharmacokinetic properties

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

The principle of perfusion scintigraphy is capillary blockade. After intravenous injection, more than 95% of the macrosalb aggregates is retained in the pulmonary arterioles and capillaries at the time of first passage through the lungs. The diameter of the macroaggregates is between 30 and 50 µm for 60%, whereby no particle is larger than 150 µm. Depending on the distribution of particle sizes, roughly every 1,000,000th capillary (diameter < 20 µm) and every 1,000th arteriole (diameter > 20 µm) is temporarily occluded. The extent of regional blockade with micro-embolisms is thus directly proportional to the regional lung perfusion at the time. Hemodynamic changes are directly related to the particle size of the technetium [^{99m}Tc] macrosalb aggregates.

The elimination of the macroaggregate particles from the lungs takes place by mechanical fragmentation through the systolic/diastolic pressure pulses within the capillaries and enzymatic breakdown with subsequent phagocytosis by the 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.

5.3 Preclinical safety data

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

The pathophysiologic mechanism responsible for toxicity is shown to be the increase of the pulmonary blood pressure. With particles from 10-50 µm 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 µm sized macrosalb are injected, where no significant pressure changes are recorded with 40 mg of less than 35 µm macrosalb particles.

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

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

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

Human albumin
Stannous chloride dihydrate
Sodium chloride

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6 or 12.

6.3 Shelf life

2 years
After reconstitution: 8 hours.

6.4 Special precautions for storage

Lyophilized product: Store in a refrigerator (2°C – 8°C)
Labelled product: Store below 25°C.
Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of the container

One vial contains 8.8 mg lyophilisate.
10 ml Type I glass vial closed with a butyl rubber stopper Type I. Pack sizes: 5, 10, 30 or 100 vials in a carton.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical requirements. Instructions on how to prepare the radiopharmaceutical are provided in Section 12.

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

7. MARKETING AUTHORISATION HOLDER

DRAXIMAGE (UK) Limited
London England EC4M 7B4

8. MARKETING AUTHORISATION NUMBER(S)

PL 29620/0001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

03/10/2007

10. DATE OF REVISION OF THE TEXT

03/10/2007

11. DOSIMETRY

Technetium [^{99m}Tc] decays with the emission of gamma radiation with energy of 140 keV and a half-life value of 6.02 hours to technetium [⁹⁹Tc], which can be regarded as being virtually stable.

The data on exposure to radiation are from the publication ICRP 80.

Absorbed dose per unit activity administered (mGy/MBq)

Organ	Adult	15 years	10 years	5 years	1 year
Adrenal gland	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
Mammary gland	0.0050	0.0056	0.0099	0.014	0.02
Gall bladder	0.0056	0.0070	0.010	0.016	0.024
Gastrointestinal tract					
Stomach wall	0.0037	0.0052	0.0080	0.012	0.020
Small intestine	0.0020	0.0026	0.0043	0.0068	0.012
Large intestine	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	0.74
Lung	0.066	0.097	0.13	0.20	0.39
Muscles	0.0028	0.0037	0.0052	0.0077	0.014
Esophagus	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 bone 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
Other tissue	0.0028	0.0036	0.0050	0.0074	0.013
Effective Dose per unit activity administered (mSv/MBq)	0.011	0.016	0.023	0.0034	0.063

The effective dosage among adults for administration of 150 MBq of activity (maximum recommended dose for planar scintigraphy) is approximately 1.7 mSv and 2.2 mSv for 200 MBq (maximum recommended dosage for SPECT scintigraphy).

The dosage absorbed in the lungs (as target organ) is thus approximately 10 mGy and in the critical organs – suprarenal glands, bladder wall, liver, pancreas and spleen – is 1.0, 1.3, 2.4, 0.8 and 0.6 mGy, respectively.

When a dosage of 200 MBq is administered, the administered dosage in the lungs as target organ is around 13 mGy; in the critical organs – suprarenal glands, bladder wall, liver, pancreas and spleen, the figures are 1.4, 1.7, 3.2, 1.1 and 0.8 mGy respectively.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Estimation of volume and pertechnetate activity in connection with the number of macrosalb particles

First step: Estimation of the labelling volume of the vial in dependence of the volume and number of the macrosalb particles per dose to be injected. The following table gives examples for injection volumes of 0.1 to 1 mL which were calculated with the following formula.

labelling volume = $\frac{\text{Number of macrosalb-particles per vial} \times \text{volume to inject}}{\text{Number of macrosalb-particles per dose to be injected}}$

Table 1: Calculation of labelling volume

Number of the macrosalb particles per dose to be injected	Volume to be injected (mL)					
	0.1	0.2	0.3	0.5	0.8	1.0
700,000	0.86	1.71	2.57	4.29	6.86	8.57
600,000	1.00	2	3	5	8	–
500,000	1.20	2.4	3.6	6	–	–
400,000	1.50	3	4.5	7.5	–	–
300,000	2	4	6	–	–	–
250,000	2.4	4.8	7.2	–	–	–
200,000	3	6	–	–	–	–
150,000	4	8	–	–	–	–
50,000	–	–	–	–	–	–
30,000	–	–	–	–	–	–

- with a mean of 6,000,000 particles per vial

Table 2: Calculation of the number of macrosalb particles to be injected

Labelling volume (mL)	Volume to be injected (mL)					
	0.1	0.2	0.3	0.5	0.8	1.0
2	300,000	600,000	900,000	1,500,000	2,400,000	3,000,000
3	200,000	400,000	600,000	1,000,000	1,600,000	2,000,000
4	150,000	300,000	450,000	750,000	1,200,000	1,500,000
5	120,000	240,000	360,000	600,000	960,000	1,200,000
6	100,000	200,000	300,000	500,000	800,000	1,000,000
7	85,714	171,429	257,143	428,571	685,714	857,143
8	75,000	150,000	225,000	375,000	600,000	750,000

- with a mean of 6,000,000 particles per vial

Second Step: Calculation of the radioactivity to be added to the vial. Here the following formula is used.

Total activity of the vial = $\frac{\text{activity to be injected} \times \text{labelled volume}}{\text{volume to inject}}$

Instructions for labelling

As the number of particles may vary from batch to batch, please consult the Simplified Reconstitution Recommendations, supplied with each kit, prior to reconstituting a vial of Macrosalb DRAXIMAGE.

The preparation of Technetium [^{99m}Tc] macrosalb injection may be accomplished under LAF (Laminar Air Flow) by the following procedure. Use aseptic procedure throughout and take precautions to minimize radiation exposure by the use of suitable shielding. Water-proof gloves should be worn during the preparation procedure.

Before reconstituting a vial it should be inspected for cracks and/or a melted plug or any other indication that the integrity of the vacuum seal has been lost.

The ^{99m}Tc pertechnetate eluate should be less than 2 hours old and should be obtained from a generator which has been eluted within the last 24 hours.

To prepare Technetium [^{99m}Tc] macrosalb injection:

- Remove the protective disc from the reaction vial and swab the closure with an alcohol swab.
- Place the vial in a suitable lead vial shield which has a minimum wall thickness of 3 mm (1/8 inch) and which has a fitted lead cap. Obtain 2 to 8 mL of sterile, non-pyrogenic Sodium Pertechnetate [^{99m}Tc] Injection Ph. Eur. using a shielded syringe.
The recommended amount of technetium ^{99m}Tc (at the time of elution) to be added to a reaction vial is 0.222 to 5.18 gigabecquerels (6 to 140 mCi). Sodium pertechnetate [^{99m}Tc] solutions containing an oxidizing agent are not suitable for use.
- Using a shielded syringe, aseptically add the sodium pertechnetate [^{99m}Tc] solution to the reaction vial, while avoiding the build-up of excessive pressure in the vial. Pressure build-up may be avoided by injecting several millilitres of pertechnetate solution into the reaction vial, then withdrawing several millilitres of nitrogen gas (present to prevent oxidation of the complex) into the syringe. The procedure is repeated as necessary until the entire amount of pertechnetate is added to the vial and normal pressure is established within the vial.
- Place the lead cap on the vial shield and mix the contents of the shielded vial by repeated gentle inversion until all the material is suspended. Avoid the formation of foam. Using proper shielding, the vial should be visually inspected to ensure that the suspension is free of foreign matter before proceeding; if it is not, the radiopharmaceutical should not be used. To ensure maximum radiolabelling allow the preparation to stand for 5 minutes after mixing.
- Assay the product in a suitable calibrator, record the radioassay information on the label which has a radiation warning symbol. Also note the time and date of preparation. Apply the label to the vial shield.
- The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochemical purity should not be less than 90%.
- Withdrawals for administration must be made aseptically using a sterile needle (18-21 gauge) and syringe. Since the vials contain nitrogen, the vials should not be vented. If repeated withdrawals are made, the replacement of the contents of the vial with air should be minimized.
- The finished preparation should be discarded after 8 hours. It should also be retained during its life in a lead vial shield with the lead cap in place.
- Any unused product or waste material should be disposed of in accordance with local requirements.

After reconstitution of the vial contents and after labelling with the eluate of a ^{99m}Tc-generator (usually 0.9 % sodium chloride) the solution will also contain, in addition to sodium chloride, tin (II) chloride: 0.1 mg. Contents are present in nitrogen atmosphere. The pH of the solution is 5.4 to 6.0.

Instructions for quality control

Non-filterable radioactivity at 5 min after labelling (consult the Ph. Eur. monograph 296):

Membrane filter 3 µm diameter pore filter

Filtered volume 200 µL

Wash solution 20 ml saline solution

The radioactivity remaining in the membrane must be ≥ 90% of the total radioactivity.