SUMMARY OF PRODUCT CHARACTERISTICS

for

VASCULOCIS
Kit for the preparation of technetium (^{99m}Tc) human albumin injection

1. NAME OF THE MEDICINAL PRODUCT

VASCULOCIS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 10 mg of human serum albumin.

The radionuclide is not part of the kit.

Excipient with known effect:
Each vial contains 3.6 mg of sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.
White lyophilisate.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) solution, the solution of technetium (^{99m}Tc) human albumin is indicated for planar radionuclide ventriculography (first-pass and equilibrium) and gated-SPECT scintigraphy of the cardiac chambers.

The following indications have been particularly documented:

- Evaluation and follow-up of patients with cardiomyopathy caused by cytotoxic drugs,
- Evaluation and follow-up of patients with cardiomyopathy and low cardiac echogenicity or poor acoustic window,
- Detection of ventricular dyssynchrony before cardiac resynchronisation therapy,
- Detection of arrhythmogenic right ventricular dysplasia (ARVD),
- Evaluation of cardiac function before cardiac or lung transplantation, and follow-up after cardiac transplant.

4.2. Posology and method of administration

Posology

Adults and elderly

The recommended activity administered to an adult of average weight (70 kg) is 800 MBq (range of 350 – 925 MBq).

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 to adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM – May 2014), using the formula below and the coefficient based on the patient's body mass (Table 1).

Recommended activity [MBq] = 56.0 x coefficient (Table 1)

Table 1

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

* In very young children (up to 1 year) a minimum dose of 80 MBq is necessary in order to obtain images of sufficient quality.

Method of administration

Multidose vial

This medicinal product should be radiolabelled before administration to the patient.
The radiolabelled solution is administered by intravenous injection.

For first-pass scintigraphic acquisition, the solution of (^{99m}Tc) human serum albumin (1 to 2 mL) should be administered rapidly as a bolus (1-2 seconds) and followed by a continuous saline bolus (10-20 mL) to flush the radionuclide bolus into the venous system.

For instructions on extemporaneous preparation of the medicinal product before administration, see section 12.
For patient preparation, see section 4.4.

Image acquisition

Scintigraphic acquisitions are gated to the electrocardiogram. Dynamic acquisitions are acquired in a planar mode during the intravenous injection of the preparation in order to capture the transit of the radiotracer in the cardiac cavities (first-pass images). The acquisition of blood-pool gated images of the heart starts 1-2 minutes after injection of the preparation (equilibrium images) and can be performed in planar or SPECT mode.

4.3. Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

4.4. Special warnings and precautions for use

Potential for hypersensitivity or anaphylactic reactions
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.

Paediatric population
For information on the use in paediatric population, see section 4.2.
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.

Specific warnings
This product is not indicated for administration in the spinal and cerebral fluid for myeloscintigraphy and cisternography.

This product contains human albumin.
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 to European Pharmacopoeia specifications by established processes.

It is strongly recommended that every time that Vasculocis 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.

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

Precautions with respect to environmental hazard are in section 6.6.

4.5. Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6. 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 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.
Breastfeeding:
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.

4.7. Effects on ability to drive and use machines

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

4.8. Undesirable effects

For safety information with respect to transmissible agents, see section 4.4.

Adverse reactions are listed below, sorted by the MedDRA System Organ Class and frequency. "Not known": cannot be estimated from the available data.

Immune system disorders
Frequency not known: hypersensitivity, face oedema.

Nervous system disorders
Frequency not known: dizziness

Cardiac disorders
Frequency not known: tachycardia

Vascular disorders
Frequency not known: circulatory collapse, vasodilatation, hypotension, flushing

Respiratory, thoracic and mediastinal disorders
Frequency not known: dyspnoea

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is5.6 mSv when the maximal recommended activity of925 MBq 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:

Danish Medicines Agency
Axel Heides Gade 1
2300 Copenhagen S
Website: www.meldenbivirkning.dk
Email: dkma@dkma.dk

4.9. Overdose

In the event of administration of a radiation overdose with technetium (^{99m}Tc) albumin no practical measure can be recommended to satisfactorily diminish tissue exposure as the technetium (^{99m}Tc) albumin is poorly eliminated in urine and faeces.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceuticals, cardiovascular system, Technetium (^{99m}Tc) compounds, ATC code: V 09 GA 04.

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

5.2. Pharmacokinetics properties

Human serum albumin is a naturally occurring component of blood. It remains within the blood stream for at least four hours.

No significant concentration of technetium (^{99m}Tc) human albumin outside the vascular space is observed, except in excretory organs (kidney, bladder).

5.3. Preclinical safety data

The product used in preclinical studies contained 10 mg of human serum albumin and 0.02 mg of stannous chloride dihydrate.

Doses equivalent to approximately 900 times the human dose of 0.14 mg/kg (126 mg/kg) cause no deaths or adverse reactions in mice and rats injected intravenously with heterologous protein.

Repeated dose toxicity studies performed in rats show no detectable variations in the general behaviour of the animals and in haematological and biochemical parameters taken into consideration after intravenous administration during 14 days of doses equivalent to approximately 50 and 100 times the human dose of 0.14 mg/kg. No evidence of pathological changes in the main organs is detected.

This medicinal product is not intended for regular or continuous administration.
Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Stannous chloride dihydrate
Sodium chloride
Concentrated hydrochloric acid (for pH adjustment)
Under a Nitrogen atmosphere

6.2. Incompatibilities

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

6.3. Shelf life

1 year.
The expiry date is indicated on the outer packaging and on each vial.
After radiolabelling: 8 hours. Do not store above 25°C after radiolabelling.

6.4. Special precautions for storage

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

15 ml, brown coloured, European Pharmacopoeia type I, drawn glass vials, closed with chlorobutyl rubber stoppers and aluminium capsules.

Pack size: 5 multidose vials.

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) human albumin and are not to be administered directly to the patient without undergoing the preparative procedure.

For instructions on extemporaneous 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 extemporaneous preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc) injection 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 or 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

CIS bio international
Route Nationale 306
BP 32
F-91192, GIF-SUR-YVETTE Cedex
France

8. MARKETING AUTHORISATION NUMBER

DK R. 1043

9. DATE OF FIRST AUTHORISATION

February 13th 1995

10. DATE OF REVISION OF THE TEXT

21. December 2021

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 energy of 140 keV and a half life of 6 hours to technetium (^{99}Tc) which, in view of its long half-life of 2.13 x 10^5 years, can be regarded as quasi stable.

According to ICRP 53, the radiation doses absorbed by the patients are the following:

	Absorbed dose per unit of administered activity (mGy/MBq)				
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.0083	0.01	0.016	0.025	0.047
Bladder wall	0.004	0.0058	0.0081	0.011	0.021
Bone surfaces	0.0089	0.012	0.022	0.036	0.071
Breast	0.0046	0.0047	0.0074	0.011	0.02
Gastrointestinal tract					
Stomach wall	0.0051	0.0065	0.01	0.014	0.025
Small intestine	0.0048	0.0058	0.0088	0.013	0.024
Upper large intestine wall	0.0047	0.006	0.0086	0.014	0.023
Lower large intestine wall	0.0042	0.0056	0.0086	0.012	0.023
Heart	0.02	0.025	0.036	0.054	0.092
Kidneys	0.0081	0.0097	0.015	0.024	0.044
Liver	0.0073	0.0087	0.014	0.021	0.037
Lungs	0.013	0.016	0.026	0.041	0.076
Ovaries	0.0044	0.0057	0.0085	0.013	0.023
Pancreas	0.0064	0.0077	0.012	0.017	0.03
Red marrow	0.0075	0.009	0.013	0.02	0.035
Spleen	0.014	0.016	0.026	0.04	0.076
Testes	0.0029	0.0039	0.0057	0.0088	0.016
Thyroid	0.0049	0.0073	0.012	0.019	0.035
Uterus	0.0048	0.0057	0.0085	0.013	0.023
Other tissue	0.004	0.0047	0.0069	0.011	0.02
Effective dose Equivalent (mSv/MBq)	**0.0079**	**0.0097**	**0.015**	**0.023**	**0.042**

According to ICRP 80 (adult effective dose of 0.0061 mSv/MBq), the effective dose resulting from the administration of a maximal recommended activity of 925 MBq for an adult weighing 70 kg is about 5.6 mSv.

For an administered activity of 925 MBq the typical radiation dose to the target organ (heart) is 18.5 mGy and the typical radiation doses to the critical organs are: adrenals: 7.7 mGy; kidneys: 7.5 mGy; liver: 6.8 mGy; lungs: 12 mGy; and spleen: 13 mGy.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Withdrawals should be performed under aseptic conditions. The vials must not be opened. After 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.

Method of preparation
Sodium pertechnetate (^{99m}Tc) injection should comply with European Pharmacopoeia specifications.

Use freshly eluted sodium pertechnetate (^{99m}Tc) solution (**less than two hours**), obtained from generators previously eluted **within the last 24 hours**.

Take a vial from the kit and put it in an appropriate lead shielding.

Using a hypodermic syringe, introduce through the rubber stopper 1 to 8 ml of sterile pyrogen-free sodium pertechnetate (^{99m}Tc) injection, activity varying as a function of the volume from 90 MBq to maximum 2.20 GBq.

Do not use a breather needle as the contents are under nitrogen.
After introduction of the volume of sodium pertechnetate (^{99m}Tc) injection, without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial.

Shake the vial carefully several times in order to dissolve the dried product, then allow to stand for about 20 minutes.

The obtained preparation is a clear and colourless solution, with a pH ranging between 2.0 and 6.5.

Before use, limpidity of the solution after preparation, pH, radioactivity and radiochemical purity should be checked.

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

Method:
Ascending paper chromatography

Materials and reagents:

- Chromatographic paper
  Whatman 1 strips of sufficient length and not less than 2.5 cm wide.

  Trace two fine lines parallel to the ends of the strips, the one being called "deposit line" at 2.5 cm, the other one being called "solvent line" at 15 cm from the "deposit line".

- Mobile phase
  Methanol/water (80/20)
- Glass tank
  Glass tank of suitable size for the chromatographic paper used, ground at the top to take a closely fitting lid.
- Miscellaneous
  Forceps, scissors, syringes, needles, appropriate counting assembly.

Procedure

1. Place into the glass tank a layer 2 cm deep of the mobile phase.
2. Apply a spot of the preparation to the "deposit line" of the paper strip using a syringe and needle and dry in air.
3. Using forceps insert the paper strip into the tank and close the lid. Lower the paper into the mobile phase and allow the solvent to migrate to the "solvent line".
4. Remove the paper strip with forceps and dry in air.
5. Determine distribution of radioactivity with an appropriate detector.
   Identify each radioactive spot by calculating the Rf. The Rf of technetium (^{99m}Tc) human albumin is 0, and that of pertechnetate ion (free (^{99m}Tc) technetium) is 0.6.
   Measure the radioactivity of each spot by integration of the peaks.

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

$$\% \text{ technetium } (^{99m}\text{Tc}) \text{ human albumin} = \frac{\text{Radioactivity of the spot at Rf 0}}{\text{Total radioactivity of the paper strip}} \times 100$$

   Calculate the percentage of free (^{99m}Tc) technetium

$$\% \text{ free } (^{99m}\text{Tc}) \text{ technetium} = \frac{\text{Radioactivity of the spot at Rf 0.6}}{\text{Total radioactivity of the paper strip}} \times 100$$

7. The percentage of technetium (^{99m}Tc) human albumin (radiochemical purity) should be at least 95 % and the percentage of free (^{99m}Tc) technetium should be no greater than 5 %.

Do not use the radiolabeled solution if the radiochemical purity is less than 95 %.