July 13, 2009

SUMMARY OF PRODUCT CHARACTERISTICS

for

Nanocoll, kit for radiopharmaceutical preparation

1. NAME OF THE MEDICINAL PRODUCT

NANOCOLL

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Human albumin colloidal particles 500 micrograms/vial

At least 95 % of human albumin colloidal particles have a diameter ≤ 80 nm.
NANOCOLL is prepared from human serum albumin derived from human blood donations tested according to the EEC Regulations and found non reactive for:

- Hepatitis B surface antigen (HBsAg)
- Antibodies to human immunodeficiency virus (anti-HIV 1/2)
- Antibodies to hepatitis C virus (anti-HCV)

NANOCOLL is reconstituted with Sodium Pertechnetate (^{99m}Tc) Injection (not included in this kit) to prepare technetium-99m albumin nanocolloid injection.

Technetium-99m decays with the emission of gamma radiation with an energy of 140 keV and a half life of 6 hours to technetium-99 which can be regarded as quasi stable.

Excipients:
Sodium: 0.30 mg/ml

For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
Powder for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

After reconstitution with Sodium Pertechnetate (^{99m}Tc) injection, the agent may be used for:

Intravenous administration:

- Bone marrow scanning. (The product is not suitable to study the haematopoietic activity of the bone marrow).
- Inflammation scanning in areas other than the abdomen.

Subcutaneous administration:

Lymphatic scanning to demonstrate integrity of the lymphatic system and differentiation of venous from lymphatic obstruction.

4.2. Posology and method of administration

Recommended activities in adults are as follows:

Intravenous administration:

- Bone marrow scanning: 185-500 MBq. Images may be acquired 45-60 minutes after administration.
- Inflammation imaging: 370-500 MBq. Dynamic imaging is performed immediately.

Static imaging comprises an early phase, 15 minutes post-injection and a washout phase, 30-60 minutes post-injection.

Subcutaneous administration:

The recommended activity for lymphoscintigraphy by single or multiple subcutaneous (interstitial) injection ranges from 18.5-110 MBq per injection site and depends on the anatomical areas to be investigated and upon the time interval between injection and imaging. The injected volume should not exceed 0.2 - 0.3 ml. A maximum volume of 0.5 ml per injection is critical.

The injection site is given subcutaneously, after checking by aspiration, that a blood vessel has not been inadvertently punctured. When imaging the lower limbs, dynamic pictures are taken immediately following injection and static imaging 30-60 minutes later.

In parasternal lymph scanning, repeated injections and additional images may be required.

Paediatric doses

The activity for children may be calculated from the recommended range of adult activity and adjusted according to body weight or surface area. However the Paediatric Task Group of the European Association of Nuclear Medicine (EANM) recommends calculating the administered activity from the body weight according to the following table.

Fraction of adult dose:

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

In very young children (up to 1 year) a minimum dose of 20 MBq (bone marrow scanning) is necessary in order to obtain images of sufficient quality.
In children, it is possible to dilute the product up to 1:50 with sodium chloride for injection.
This agent is not intended for regular or continuous administration.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients

During pregnancy, lymphoscintigraphy involving the pelvis is strictly contraindicated due to the accumulation in lymph nodes.

4.4 Special warnings and precautions for use

The possibility of hypersensitivity including serious, life-threatening, fatal anaphylactic/anaphylactoid reactions should always be considered.

Lymphoscintigraphy is not advised in patients with total lymphatic obstruction because of the potential radiation hazard at injection sites.

Standard measures for preventing transmission of infections from pharmaceuticals made of human blood or plasma, include selection of donators, test of individual donators and plasma pools for finding specific infective agents, and effective manufacturing steps for inactivation/elimination of virus as a part of manufacturing process as well. In spite of that, the risk of transmission of infectious agents cannot be eliminated completely, as long as pharmaceuticals made of human blood or plasma are used. This also applies to new virus of unknown nature and other pathogens as well.

There are no reports of virus transmission in connection with albumin, made in accordance with specifications in Ph. Eur. and in accordance with routine processes.

It is strongly recommended that the product name and batch number are stated every time Nanocoll is given to a patient, in order to maintain a connection between the patient and the product's batch number.

Before reconstitution Nanocoll contains 0.30 mg sodium/vial. This needs to be taken into considerations for patients on a controlled sodium diet.

4.5 Interaction with other medicinal products and other forms of interaction

Iodinated contrast media used in lymphoangiography may interfere with lymphatic scanning using technetium-99m albumin nanocolloid.

4.6 Pregnancy and lactation

Pregnancy

During pregnancy the subcutaneous administration of technetium-99m albumin nanocolloid for lymphoscintigraphy is strictly contraindicated, due to the possible accumulation in pelvic lymph nodes.
Only imperative investigations should be carried out during pregnancy, when the likely benefit exceeds the risk incurred by mother and foetus.
Radionuclide procedures carried out on pregnant women also involve radiation doses to the foetus.

Dose to the uterus arising for intravenous administration of 500 MBq of technetium-99m albumin nanocolloid is 0.9 mGy. Dose to the uterus above 0.5 mGy will be regarded as a potential risk to the foetus.

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.

Lactation
If the administration is considered necessary, breast-feeding should be interrupted for 13 hours and the expressed feeds discarded.
Breast-feeds should be banked prior to injection.
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.

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

4.8 Undesirable effects

For each patient, exposure to ionising 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 result. For safety with respect to transmissible agents see section 4.4.

Congenital, familial and genetic disorders Frequency not known (cannot be estimated from the available data)	Hereditary defects.
Neoplasms benign, malignant and unspecified (including cysts and polyps) Frequency not known (cannot be estimated from the available data)	Cancer induction.
Immune system disorders Frequency not known (cannot be estimated from the available data)	Hypersensitivity reactions (including very rare life-threatening anaphylaxis).

Occasionally hypersensitivity reactions (including very rare life-threatening anaphylaxis) may occur.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evi-

dence suggests that these adverse effects will occur with low frequency because of the low radiation doses incurred.

For most diagnostic investigations using a nuclear medicine procedure the effective dose is 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9 Overdose

In the event of an overdose of radioactivity being administered when using technetium-99m albumin nanocolloid, no practical measure can be recommended to satisfactorily diminish tissue exposure as the label is poorly eliminated in urine and faeces.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Technetium (^{99m}Tc), particles and colloids
ATC-code: V09DB01

At the chemical concentrations and activities used for diagnostic procedures technetium-99m albumin nanocolloid does not appear to exert any pharmacodynamic effects.

5.2 Pharmacokinetic properties

Reticuloendothelial cells in liver, spleen as well as in bone marrow are responsible for blood clearance after intravenous injection. A small fraction of technetium-99m radioactivity passes through kidneys and is eliminated in urine.
The maximum concentration in the liver and spleen is reached after about 30 minutes, but in the bone marrow after only 6 minutes.
The proteolytic breakdown of the colloid begins immediately after its uptake by the reticuloendothelial system (RES), the products of degradation being excreted through the kidneys into the bladder.
After subcutaneous injection into connective tissue, 30-40 % of the administered technetium-99m albumin colloidal particles (less than 100 nm) are filtered into lymphatic capillaries whose main function is the drainage of proteins from the interstitial fluid back into the blood pool. The technetium-99m albumin colloidal particles are then transported along the lymphatic vessels to regional lymph nodes and main lymphatic vessels, and are finally trapped into the reticular cells of functionary lymph nodes. A fraction of the injected dose is phagocytised by histiocytes at the injection site. Another fraction appears in the blood and accumulates mainly in the RES of the liver, spleen and bone marrow; faint traces are eliminated via the kidneys.

5.3 Preclinical safety data

No animal death and no gross pathological changes at necropsy were noted after intravenous injection of 800 and 950 mg in mice and rats respectively.
No local reactions were observed in either mice or rats subcutaneously injected with 1g/kg. These doses correspond to the contents of several tens of vials per kg body weight, compared to the human albumin colloid dose of 7 micrograms/kg generally used in nuclear medicine for diagnosis.
Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride, dihydrate
Glucose, anhydrous
Poloxamer 238
Sodium phosphate, dibasic, anhydrous
Sodium phytate, anhydrous

6.2 Incompatibilities

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

6.3 Shelf life

Kit before reconstitution: 12 months from the date of manufacture.

Reconstituted product: should be used within 6 hours after labelling.
Store below 25ºC. Do not refrigerate or freeze.

6.4 Special precautions for storage

Store in a refrigerator (2-8°C).

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

For storage conditions of the reconstituted product, see section 6.3.

6.5 Nature and contents of the container

10 ml, Type I Ph.Eur., glass vials sealed by bromobutyl rubber stoppers and metal flip off caps, placed in a polystyrene tray and a package insert, inserted in a cardboard box.

Pack size:
Each kit contains 5 vials.

6.6 Special precautions for disposal and other handling

Normal safety precautions for handling radioactive materials should be observed. After use, all materials associated with the preparation and administration of radiopharmaceuticals, including any unused product and its container, should be decontaminated or treated as radioactive waste and disposed of in accordance with the conditions specified by the local competent authority. Contaminated material must be disposed of as radioactive waste via an authorised route.

7. MARKETING AUTHORISATION HOLDER

GE Healthcare S.r.l.
Via Galeno, 36
20126 - Milan - Italy

Representative
GE Healthcare A/S
Huginsvej 8
3400 Hillerød

8. MARKETING AUTHORISATION NUMBER

DK R 1107

9. DATE OF FIRST AUTHORISATION

20. June 1995

10. DATE OF REVISION OF THE TEXT

July 13, 2009

11. DOSIMETRY

The radiation doses absorbed by a patient weighing 70 kg, after intravenous injection of ^{99m}Tc-human albumin colloidal particles, are reported hereafter.

Organ	Absorbed dose µGy/MBq
Liver	78
Urinary bladder (wall)	25
Spleen	18
Bone marrow (red)	14
Ovaries	3.2
Testes	1.1
Whole body	5.1

For this product the effective dose equivalent resulting of an administered activity of 500 MBq is 2.5 mSv (per 70 kg individual).
For an administered activity of 500 MBq the typical radiation dose to the critical organ (liver) is 23 mGy and the typical radiation dose to the target organ (red bone marrow) is 0.75 mGy.
The radiation doses absorbed by a patient weighing 70 kg, after subcutaneous injection of ^{99m}Tc-human albumin colloidal particles, are reported hereafter.

Organ	Absorbed dose µGy/MBq
Injection site	12000
Lymph nodes	590
Liver	16
Urinary bladder (wall)	9.7
Spleen	4.1
Bone marrow (red)	5.7
Ovaries	5.9
Testes	3.5
Whole body	4.6

For this product the effective dose equivalent resulting of an administered activity of 110 MBq is 0.44 mSv (per 70 kg individual).
For an administered activity of 110 MBq the typical radiation dose to the target organ (lymph nodes) is 8.1 mGy and to the critical organ (injection site) 183 mGy.
The radiation dose estimation for a number of organs is based on MIRD reference man and MIRD S values, and has been calculated from biological data of organ uptake and blood clearance

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

This radiopharmaceutical may be received, used and administered only by authorised persons in designated clinical settings. Its receipt, storage, use, transfer and disposal are subject to the regulation and/or appropriate licenses of local competent official organisations (see section 6.6).

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

Method of preparation

- Place a vial containing the albumin colloidal particles in a convenient lead shield.
- Aseptically introduce into the vial 1-5 ml Sodium Pertechnetate (^{99m}Tc) Injection Ph. Eur. with a radioactivity ranging from 185 to 5550 MBq (5 to 150 mCi).
- Do not use a breather needle.
- Relieve the excess of pressure in the vial by simply withdrawing an equal volume of gas in the syringe.
- Invert carefully a few times to dissolve the contents of the vial.
- Then allow standing for 30 min at room temperature (15°C -25°C).
- Shake before withdrawing a dose.
- In no case should the preparation be left in contact with air.

The disposal of waste should be in accordance with national and international guidelines.

Quality control

A – RCP by ascending paper chromatography

Support:	paper Whatman No. 1
Solvent:	methanol:water 85:15 v/v
Time:	1 hour
^{99m}Tc (nanocolloid):	≥ 95 %
Rf:	0,0 %

B - RCP by ascending chromatopgraphy on ITLC-SG:

Support:	ITLC-SG
Solvent:	methanol:water 85:15 v/v
Time:	5-10 min
^{99m}Tc (nanocolloid):	≥ 95 %
Rf:	0,0 % ± 0,1 %