2) Early to intermediate diffuse parenchymal liver disease

Organ	Absorbed dose per unit activity administered [mGy/MBq]
Adrenals	9.9E-03
Bladder wall	1.4E-03
Bone surfaces	8.2E-03
Breast	2.6E-03
GI tract	
Stomach wall	8.1E-03
Small intestine	4.4E-03
ULI wall	5.3E-03
LLI wall	2.4E-03
Kidneys	1.1E-02
Liver	4.0E-02
Lungs	5.2E-03
Ovaries	2.7E-03
Pancreas	1.5E-02
Red marrow	1.5E-02
Spleen	1.0E-01
Testes	8.6E-04
Thyroid	1.0E-03
Uterus	2.4E-03
Other tissue	3.0E-03
Effective dose Equivalent [mSv/MBq]	**1.4E-02**

In early to intermediate diffuse parenchymal liver disease, the effective dose equivalent resulting from an administered activity of 185 MBq technetium-99m colloidal tin is 2.6 mSv.

3) Intermediate to advanced diffuse parenchymal liver disease

Organ	Absorbed dose per unit activity administered [mGy/MBq]
Adrenals	9.8E-03
Bladder wall	1.6E-03
Bone surfaces	1.2E-02
Breast	2.4E-03
GI tract	
Stomach wall	9.8E-03
Small intestine	4.6E-03
ULI wall	4.9E-03
LLI wall	3.1E-03
Kidneys	1.1E-02
Liver	4.2E-02
Lungs	4.8E-03
Ovaries	3.3E-03
Pancreas	1.8E-02
Red marrow	2.3E-02
Spleen	1.4E-01
Testes	9.5E-04
Thyroid	1.1E-03
Uterus	2.8E-03
Other tissue	3.1E-03
Effective dose (E) [mSv/MBq]	**1.7E-02**

In intermediate to advanced diffuse parenchymal liver disease, the effective dose equivalent resulting from an administered activity of 185 MBq technetium-99m colloidal tin is 3.1 mSv.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Radiopharmaceuticals should be prepared by the user in a manner which satisfies both radiation safety and pharmaceutical quality requirements. Appropriate aseptic precautions should be taken.

As with any pharmaceutical product, if at any time in the preparation of this product the integrity of this vial is compromised, the product should not be used. Therefore, prior to the radiolabelling procedure carefully inspect the vial for the presence of damage, in particular cracks.

Caution
During preparation of product do not use syringes with rubber parts.

Method of preparation of the final dosage form for injection

Use aseptic technique throughout.
• Place the kit vial containing the lyophilisate in an appropriate radioprotective shield.
• Using a syringe inject (by piercing the rubber stopper) about 5 ml of eluate of sodium pertechnetate ^{99m}Tc (or eluate with 100-1000 MBq activity range pre-diluted with sterile saline) into the vial containing lyophilisate.
• Using the same syringe relieve the excess of pressure in the vial by withdrawing the equivalent volume of gas.
• Shake carefully the contents of the vial preventing the solution from contact with rubber stopper until complete dissolution of the powder (1 min). Incubate the solution for 20 minutes at room temperature. Keep the vial in the shield all the time.
• The resultant solution is a ready to use solution for injection. ^{99m}Tc-Colloid may be used within 4 hours after completion of labelling procedure when stored at a temperature below 25°C.

Radioactivity of the preparation should be measured immediately before administration.

Instruction for quality control of the radiopharmaceutical ^{99m}Tc-Colloid

Determination of radiochemical purity by Thin Layer Chromatography

Materials
- TLC silica gel coated glass-fibre plates support
- 0.9% sodium chloride solution
- Suitable radiation detector
- Chromatographic chamber

Method
- Apply 2-5 µl of the examined solution at about 1.5 cm from the bottom of a chromatographic plate.
- Place the plate in the chromatographic chamber containing approximately 1 cm high layer of sodium chloride 0.9%.
- Develop the chromatogram until the solvent front moves about 10-15 cm from the starting line (for approximately 10 min.).
- Remove the plate and allow it to air-dry.
- Determine the radioactivity distribution on the plate by scanning the chromatogram with a suitable radiation detector or cut the plate in two pieces in the middle of development path and measure each piece activity with an appropriate radiation detector.
- Identify radioactivity spots according to their R_f value:

  R_f = 0.0 - 0.1 - complex ^{99m}Tc –Colloid remains at the starting line

  R_f = 0.9 - 1.0 - free, unbound pertechnetate $^{99m}TcO_4^-$ migrates with the solvent front

- Calculate the % radiochemical purity as:

  % technetium (Tc-99m) colloid = Activity of the lower part (R_f=0.0-0.1) / Activity sum of all parts and multiplied by 100.

- Radiochemical purity should be ≥ 95%; otherwise the preparation should be discarded.

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Location: Moldova

POLATOM

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PoltechColloid, 0.17 mg
Kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
Stannous chloride dihydrate 0.17 mg
For a full list of excipients - see section 6.1.
The radionuclide is not part of the kit.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
Lyophilisate for solution for injection
White powder

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
Technetium [^{99m}Tc] colloidal tin injection is used for scintigraphic diagnostics of reticuloendothelial system of liver and spleen.

4.2 Posology and method of administration

Product intended for preparation of radiopharmaceutical technetium [^{99m}Tc] colloidal tin injection for intravenous administration.
This radiopharmaceutical may be used only by authorized persons. Safety precautions for careful handling this radiopharmaceutical should be observed.
The solution of the radiopharmaceutical ^{99m}Tc-Colloid, obtained by reconstitution of lyophilisate in 5 ml of sterile, bacterial endotoxins and oxidant free eluate (derived from ^{99}Mo/^{99m}Tc generator) with activity of 100-1000 MBq, is administered intravenously for diagnostic purposes. For instructions for preparation of radiopharmaceutical before administration, see section 12.

Posology
One vial of the product labelled with ^{99m}Tc may be used for examinations of several patients.

Patient preparation
There is no special requirements for patient preparation.

Adults
The activity recommended for examination of a single adult patient ranges from 150 to 200 MBq of ^{99m}Tc-Colloid, however depending on indications other doses may be justifiable.

Elderly population
Literature data does not indicate the need for dosage adjustment.

Paediatric population
The use of the product in paediatric patients has to be considered carefully, based upon clinical needs and assessment of the risk/benefit ratio in this patient group. The activity for children may be calculated by modifying the adult activity according to body weight or body surface of the child.

According to recommendations of The Paediatric Task Group of the European Association of Nuclear Medicine (EANM) the paediatric dose is a part of adult dose and is calculated based on the body weight of the child according to the following table:

Body weight of the child	Dose (part of adult dose)	Body weight of the child	Dose (part of adult dose)
3 kg	0.10	32 kg	0.65
4 kg	0.14	34 kg	0.68
6 kg	0.19	36 kg	0.71
8 kg	0.23	38 kg	0.73
10 kg	0.27	40 kg	0.76
12 kg	0.32	42 kg	0.78
14 kg	0.36	44 kg	0.80
16 kg	0.40	46 kg	0.82
18 kg	0.44	48 kg	0.85
20 kg	0.46	50 kg	0.88
22 kg	0.50	52 - 54 kg	0.90
24 kg	0.53	56 - 58 kg	0.92
26 kg	0.56	60 - 62 kg	0.96
28 kg	0.58	64 - 66 kg	0.98
30 kg	0.62	68 kg	0.99

In very young children (up to 1 year) a minimum dose of 15 MBq is necessary to obtain images of sufficient quality.

In light of the European Directive 97/43/Euratom and current practice throughout Europe, the above activities should be considered only as a general indication. It should be noted that in each country nuclear medicine physicians should respect the diagnostic reference levels (DRL) and the rules laid down by the local legislation. The injection of activities greater than local DRLs should be justified.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

For each patient, the radiation exposure must be justifiable by the expected benefits resulting from diagnostic procedure using the radiopharmaceutical. The activity administered should in every case be as low as reasonably achievable to obtain the required diagnostic information.

Pregnancy, see section 4.6.
Children and adolescents, see section 4.2.

This medicinal product contains sodium (ap. 0.55 mg/vial). This should be taken into account in patient on low sodium diet.

4.5 Interactions with other medicinal products and other forms of interaction

Drugs known to be associated with short-term or long-term hepatotoxicity, such as cancer chemotherapy, contraceptives, tetracyclines and drugs which may affect hepatic blood flow, such as certain anaesthetics, may be expected to affect the biodistribution patterns of radiolabelled colloids.

4.6 Fertility, pregnancy and lactation

Pregnancy
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 diagnostic techniques not using ionising radiation (if there are any) should be offered to the patient.

Radionuclide procedures carried out in 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 administration of the radiopharmaceutical to a mother who is breastfeeding, consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding and as to whether the most appropriate choice of radiopharmaceuticals has been made. If the administration of the radiopharmaceutical is considered necessary breastfeeding should be interrupted for 12 hours and the expressed feeds discarded.

It is usual to advise that breastfeeding can be restarted when the radioactivity level in the milk will not result in a radiation dose to the child greater than 1 mSv. Close contact with infants should be restricted during this period.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

For each patient, exposure to ionising radiation must be justified 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.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations the current evidence suggests that these adverse reactions are expected to occur with a low probability.
For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (effective dose/ EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

The frequency of adverse reactions reported after administration of the product is presented in the table below.

Undesirable effects	Frequency
Investigations: lowered blood pressure	Frequency not known (cannot be estimated from the available data)
Cardiac disorders: bradycardia	Frequency not known (cannot be estimated from the available data)
Congenital, familial and genetic disorders: hereditary defects	Frequency not known (cannot be estimated from the available data)
Nervous system disorders: vasomotor problems	Frequency not known (cannot be estimated from the available data)
Respiratory, thoracic and mediastinal disorders: shortness of breath, bronchospasms	Frequency not known (cannot be estimated from the available data)
Skin and subcutaneous tissue disorders: angioedema, cutaneous reactions	Frequency not known (cannot be estimated from the available data)
Neoplasms benign, malignant and unspecified (including cysts and polyps): cancer induction	Frequency not known (cannot be estimated from the available data)
General disorders and administration site conditions: malaise, central chest or back pain	Frequency not known (cannot be estimated from the available data)

The majority of these reactions have been relatively mild but supportive treatment and/or an antihistamine drug administration may be required.

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.
Adverse reactions may be reported to Marketing Authorisation Holder.

4.9 Overdose

The risk of overdose in case of diagnostic doses can be neglected.
No specific therapy is possible in the event of the administration of an overdose.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: diagnostic radiopharmaceuticals, hepatic and reticuloendothelial system, technetium (^{99m}Tc), particles and colloids, ATC code: V09DB04.

At doses used for diagnostic procedures, technetium (^{99m}Tc) colloidal tin does not appear to have any pharmacodynamic activity.

5.2 Pharmacokinetic properties

The preparation belongs to the group of radioactive colloids which accumulate in the liver and spleen (in the reticuloendothelial system) after intravenous administration.
Small amounts of radioactive colloids are taken up by the bone marrow and other organs.

Increased uptake in the spleen, lungs and bone marrow may indicate diffuse liver disease.

After intravenous administration ^{99m}Tc-Colloid is rapidly eliminated from the blood ($T_{1/2}$ = 1.5 - 2 min) and relatively rapidly accumulates in the liver and spleen. Reduction in counts over the heart is associated with relatively rapid increase in activity in the liver (T_{max} = 10.9 min) and spleen (T_{max} = 16 min).

An increased accumulation of radiocolloid in these organs remains to the end of measurements. The biological elimination half-life determined on the basis of measurement of decreasing radioactivity level over the liver and spleen is similar to the 6.02 hours half-life of technetium-99m.

Due to long effective hepatic elimination time ^{99m}Tc-Colloid allows to perform static imaging, visualizing the shape and size of the liver.

5.3 Preclinical safety data

The preparation is characterised by very low toxicity. LD_{50} (determined by Litchfield and Wilcoxon method) is 235 mg/kg b.w.

Low toxicity of the complex with technetium-99m allows safe administration of diagnostic doses of ^{99m}Tc-Colloid to all patients.
No immunization effects were observed in patients.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium fluoride
Povidone
Nitrogen

6.2 Incompatibilities

No data.

6.3 Shelf life

Shelf life of the kit is 1 year.
The radiolabelled product ^{99m}Tc-Colloid should be administered within 4 hours of preparation.

Radiochemical purity and stability data of preparation refer to this time at a temperature below 25°C.

6.4 Special precautions for storage

Store in a refrigerator (2°C- 8°C).
During transportation (not longer than 7 days) up to 35°C.

Expiry date is given on the label.

Shelf life after reconstitution and labelling with sodium pertechnetate (^{99m}Tc) solution: up to 4 hours at a temperature below 25°C in a suitable radiation lead shield.

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

6.5 Nature and contents of container

10 ml multi-dose glass vials sealed with a rubber stopper and aluminium cap in cardboard box.
3 vials
6 vials

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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 radiopharmaceutical and are not to be administered directly to the patient without first undergoing the preparative procedure.
The content of the kit before extemporary preparation is not radioactive. However, after sodium ^{99m}Tc-pertechnetate solution is added, adequate shielding of the final preparation must be maintained.
If any time in the preparation of this product the integrity of this vial is compromised it should not be used.
The administration of radiopharmaceuticals creates risk for other persons from external radiation or contamination from spills of urine, vomits, etc. 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.
Instruction for preparation of the radiopharmaceutical - see section 12.

7. MARKETING AUTHORISATION HOLDER

Narodowe Centrum Badań Jądrowych
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Phone: +48 22 7180700
Fax: +48 22 7180350
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8. MARKETING AUTHORISATION NUMBER
Marketing authorisation number: R/3267

9. DATE OF FIRST AUTHORISATION/RENEVAL OF AUTHORISATION
Date of first authorisation: 22.12.1999
Date of latest renewal: 12.08.2013

10. DATE OF REVISION OF THE TEXT

12.08.2013

11. DOSIMETRY

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

Absorbed radiation dose estimates following intravenous administration technetium [^{99m}Tc] colloidal tin injection are given for three liver conditions:

1) Normal liver
2) Early to intermediate diffuse parenchymal liver disease
3) Intermediate to advanced diffuse parenchymal liver disease

The data listed below are from publication 80 of the ICRP (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1998) for normal liver and from ICRP 53 (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1987) for early to intermediate diffuse parenchymal liver disease and for intermediate to advanced diffuse parenchymal liver disease:

1) Normal liver

In normal liver function, the effective dose equivalent resulting from an administered activity of 185 MBq technetium-99m colloidal tin to a patient of 70 kg body weight is 1.7 mSv.

The tables below show the dosimetry as calculated according to the publication 53 of the ICRP (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1987).

Absorbed dose per unit activity administered [mGy/MBq]					
Organ	**Adult**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	1.2E-02	1.5E-02	2.1E-02	2.8E-02	4.2E-02
Bladder	1.1E-03	1.6E-03	2.7E-03	5.7E-03	9.4E-03
Bone surfaces	8.7E-03	1.1E-02	1.8E-02	3.0E-02	6.9E-02
Brain	6.7E-04	8.8E-04	1.3E-03	2.1E-03	4.1E-03
Breast	2.1E-03	2.7E-03	4.6E-03	7.2E-03	1.3E-02
Gall bladder	2.0E-02	2.3E-02	3.1E-02	5.0E-02	8.4E-02
GI-tract					
Stomach	6.4E-03	8.2E-03	1.3E-02	2.1E-02	3.5E-02
Small intestine	4.0E-03	5.1E-03	8.9E-03	1.4E-02	2.4E-02
Colon	3.8E-03	4.8E-03	8.5E-03	1.5E-02	2.4E-02
ULI	5.5E-03	6.8E-03	1.2E-02	2.1E-02	3.4E-02
LLI	1.6E-03	2.2E-03	3.8E-03	6.1E-03	1.1E-02
Heart	6.5E-03	8.3E-03	1.2E-02	1.7E-02	3.0E-02
Kidneys	9.5E-03	1.2E-02	1.7E-02	2.4E-02	3.5E-02
Liver	7.1E-02	9.1E-02	1.3E-01	1.9E-01	3.4E-01
Lungs	5.9E-03	7.5E-03	1.0E-02	1.5E-02	2.5E-02
Muscles	2.7E-03	3.4E-03	4.9E-03	7.2E-03	1.3E-02
Oesophagus	2.1E-03	2.7E-03	3.7E-03	5.7E-03	9.8E-03
Ovaries	2.2E-03	2.9E-03	4.9E-03	7.9E-03	1.4E-02
Pancreas	1.3E-02	1.7E-02	2.5E-02	3.7E-02	5.9E-02
Red marrow	1.1E-02	1.2E-02	1.9E-02	3.2E-02	6.4E-02
Skin	1.3E-03	1.6E-03	2.5E-03	4.0E-03	7.6E-03
Spleen	7.5E-02	1.1E-01	1.6E-01	2.4E-01	4.3E-01
Testes	5.6E-04	7.7E-04	1.3E-03	2.3E-03	4.5E-03
Thymus	2.1E-03	2.7E-03	3.7E-03	5.7E-03	9.8E-03
Thyroid	9.3E-04	1.2E-03	2.0E-03	3.5E-03	6.5E-03
Uterus	1.9E-03	2.5E-03	4.4E-03	7.3E-03	1.4E-02
Remaining organs	2.7E-03	3.4E-03	4.9E-03	7.1E-03	1.2E-02
Effective dose [mSv/MBq]	**9.4E-03**	**1.2E-02**	**1.8E-02**	**2.8E-02**	**5.0E-02**