Absorbed dose per unit administered activity [mGy/MBq]					
Organ	**Adults**	**15 years**	**10 years**	**5 years**	**1 year**
Adrenals	0.012	0.016	0.024	0.035	0.060
Bladder	0.018	0.023	0.029	0.031	0.057
Bone surfaces	0.0050	0.0062	0.0092	0.014	0.026
Brain	0.0012	0.0015	0.0025	0.0040	0.0072
Breast	0.0013	0.0018	0.0028	0.0045	0.0084
Gall bladder	0.0083	0.010	0.014	0.022	0.031
Gastrointestinal tract					
Stomach	0.0052	0.0063	0.010	0.014	0.020
Small intestine	0.0050	0.0064	0.010	0.014	0.024
Colon	0.0043	0.0055	0.0082	0.012	0.020
(ULI	0.0050	0.0064	0.0095	0.014	0.023
(LLI	0.0033	0.0043	0.0065	0.0096	0.016
Heart	0.0030	0.0038	0.0058	0.0086	0.014
Kidneys	0.18	0.22	0.30	0.43	0.76
Liver	0.0095	0.012	0.018	0.025	0.041
Lungs	0.0025	0.0035	0.0052	0.0080	0.015
Muscles	0.0029	0.0036	0.0052	0.0077	0.014
Oesophagus	0.0017	0.0023	0.0034	0.0054	0.0094
Ovaries	0.0035	0.0047	0.0070	0.011	0.019
Pancreas	0.0090	0.011	0.016	0.023	0.037
Red marrow	0.0039	0.0047	0.0068	0.0090	0.014
Skin	0.0015	0.0018	0.0029	0.0045	0.0085
Spleen	0.013	0.017	0.026	0.038	0.061
Testes	0.0018	0.0024	0.0037	0.0053	0.010
Thymus	0.0017	0.0023	0.0034	0.0054	0.0094
Thyroid	0.0015	0.0019	0.0031	0.0052	0.0094
Uterus	0.0045	0.0056	0.0083	0.011	0.019
Remaining organs	0.0029	0.0037	0.0052	0.0077	0.014
Effective dose [mSV/MBq]	**0.0088**	**0.011**	**0.015**	**0.021**	**0.037**

The effective dose equivalent resulting from an administered activity of 150 MBq to a patient of 70 kg body weight is 1.32 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.

PoltechDMSA is designed for labelling with technetium-99m as eluate of sodium pertechnetate (^{99m}Tc) solution obtained from the ^{99}Mo/^{99m}Tc radionuclide generator. The labelling procedure should ensure sterility of the preparation.

- 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) solution (or eluate with desired activity pre-diluted with sterile saline) into the vial containing lyophilized product.
- Using the same syringe relieve the excess of pressure in the vial by withdrawing the equivalent volume of gas.
- Shake the contents of the vial until complete dissolution of the powder (about 1 - 2 min.). Keep the vial in the shield all the time.
- The received solution is a ready-to-use solution for injection. ^{99m}Tc-DMSA preparation should be used within 4 hours after completing the labelling procedure.

Regulations for safety of work at exposure to ionising radiation should be strictly observed during preparation and administration of radiopharmaceutical.

Instruction for quality control of radiopharmaceutical

Radiochemical purity measurement:

by Thin Layer Chromatography according to Ph.Eur. Monograph 0643:

ITLC-SG plates (silica gel coated glass-fiber plates); developing solution: methyl ethyl ketone (MEK).

Under these conditions:

- ^{99m}Tc-DMSA complex remains at the origin (R_f = 0.0)
- free, non-bound pertechnetate $^{99m}TcO_4^-$ migrates with the solvent front (R_f = 0.9 - 1.0).

POLATOM

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PoltechDMSA, 1 mg,

kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 vial contains:
meso-2,3-dimercaptosuccinic acid (DMSA) 1 mg
The radionuclide is not part of the kit.
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation
Lyophilisate for solution for injection

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
The radiopharmaceutical ^{99m}Tc-DMSA is intended for renal scintigraphic examination, in particular:
- static renal imaging,
- location of kidneys, determination of functional renal mass,
- morphological studies of renal cortex, determination of relative individual kidney function.

4.2 Posology and method of administration

Product intended for intravenous administration.
This radiopharmaceutical may be used only by authorised persons. Safety precautions for careful handling this radiopharmaceutical should be observed.
The radiopharmaceutical ^{99m}Tc-DMSA is administered intravenously after labelling with sterile, oxidant-free eluate of sodium pertechnetate (^{99m}Tc) solution from a radionuclide generator ^{99}Mo/^{99m}Tc, in accordance with the labelling instructions – see section 12.
For patient preparation – see section 4.4.
For radiolabelling of one kit vial the 5 ml of sodium pertechnetate (^{99m}Tc) solution with activity of 100 - 7400 MBq should be used. This amount is sufficient to perform the examination in several adult patients.

Image acquisition

The image acquisitions may be performed two to three hours post-injection. If significant hydronephrosis exists late images or furosemide injection may then be useful (4 to 24 hours).

Posology

Adults

The activity recommended for a single examination in adult patient ranges from 75 to150 MBq. However depending on indications a higher administered activity may be justifiable.

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 activity for children is adjusted according to body weight or surface area.

Pediatric activity (MBq) =
Adult dosage (MBq) x Child weight (kg) / 70
Pediatric activity (MBq) =
Adult dosage (MBq) x Child body surface (m^2) / 1.73

The activities to be administered to children and adolescents may be calculated according to the recommendations of the European Association of Nuclear Medicine (EANM) paediatric dosage card; the activity administered to children and to adolescents may be calculated by multiplying a baseline activity (for calculation purposes) by the weight-dependent multiples given in the table below.

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 15 MBq is necessary in order to obtain images of sufficient quality.

Patients with renal impairment

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

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

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.
Pregnancy, see section 4.6.

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.
In patients with renal impairment careful consideration of the indication is required since an increased exposure is possible in these patients. This must be taken into account when calculating the activity to be administered – see section 11.

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.
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.
The content of the vial is intended for preparation of radiopharmaceutical ^{99m}Tc-DMSA and may be administered to the patient only after completion of labelling procedure.

Specific warnings

Tubular defects such as the Fanconi syndrome or nephronophtisis may result in poor renal visualization (defective binding of the isotope within the tubular cell and urinary excretion).

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

4.5 Interactions with other medicinal products and other forms of interaction

Interference with the acid-base balance, e.g. by ammonium chloride and sodium bicarbonate, results in vivo in a change in valency of the technetium complex (^{99m}Tc)-DMSA - and consequently a reduced accumulation of this complex in the adrenal cortex in context of a marked concentration in the liver and faster urine excretion.

Mannitol causes dehydration and therefore a reduction in extraction of ^{99m}Tc-DMSA to the kidney.
ACE inhibitors may cause reversible failure of tubule function as a result of the reduction in filtration pressure in a kidney that is affected by renal artery stenosis. This in turn leads to reduced renal concentration of DMSA (^{99m}Tc) technetium.

Experimental research in animals has demonstrated that chemotherapy with methotrexate, cyclophosphamide or vincristine can affect the biodistribution of DMSA (^{99m}Tc) technetium.

4.6 Fertility, 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.
Where uncertainity exists it is important that the radiation exposure should be the minimum consistent with achieving the desired clinical information. 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.
Administration of 150 MBq of the preparation to a patient results in an absorbed dose to the uterus of 0.675 mGy. Doses above 0.5 mGy would be regarded as a potential risk for the foetus.

Breastfeeding
Before administering radiopharmaceuticals 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 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, breastfeeding should be interrupted for 4 hours and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Information on adverse reactions is available from spontaneous reporting. The reports describe anaphylactoid, vasovagal and injection site reactions which were mild to moderate and usually resolved with either no or symptomatic treatment.

Anaphylactoid reactions
Reported anaphylactoid reactions were mild to moderate, however the occurrence of severe reactions cannot be excluded. Appropriate instruments (including endotracheal tube and ventilator) and medications should be to hand so as to be able to react immediately in an emergency.

Vasovagal reactions
Vasovagal reactions are most probably caused by the procedure itself, especially in anxious patients, but a contribution of the product cannot be excluded.

Injection site reactions
Local reactions at the injection site may include rashes, swelling, inflammation and edema. In most cases such reactions are probably caused by extravasation. Extended extravasation may necessitate surgical treatment.

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

Undesirable effects	**Frequency**
Immune system disorders: anaphylactoid reactions: rash, pruritus, urticaria, erythema, hyperhidrosis, periorbital oedema, conjunctivitis, laryngeal oedema, pharyngeal oedema, cough, dyspnoea, abdominal pain, vomiting, nausea, salivary hypersecretion, tongue oedema, hypotension, flushing	Frequency not known (cannot be estimated from the available data)
Nervous system disorders: vasovagal reactions: syncope, hypotension, headache, dizziness, pallor, asthenia, fatigue	Frequency not known (cannot be estimated from the available data)
General disorders and administration site conditions: injection site reaction	Frequency not known (cannot be estimated from the available data)
Neoplasms benign and malignant (incl. cysts and polyps): cancer induction*	Frequency not known (cannot be estimated from the available data)
Congenital and familial / genetic disorders: hereditary defects*	Frequency not known (cannot be estimated from the available data)

*linked with ionising radiation

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.

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

In the event of the administration of a radiation overdose with ^{99m}Tc-DMSA injection, the absorbed dose to the patient should be reduced where possible by increasing the elimination of the radionuclide from the body by forced diuresis and frequent bladder voiding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: diagnostic radiopharmaceutical, technetium (^{99m}Tc) compounds,
ATC code: V09CA02

At the chemical concentrations of radiopharmaceutical and excipients used for diagnostic procedures ^{99m}Tc-DMSA does not appear to exert any pharmacodynamic effect.

5.2 Pharmacokinetic properties

PoltechDMSA is intended for technetium-^{99m}Tc labelling.

Distribution
^{99m}Tc- DMSA localizes in high concentrations in the renal cortex. Maximal localization occurs within 3 - 6 hours after intravenous injection, with about 40 - 50% of the dose retained in the kidneys. Less than 3% of the administered dose localizes in the liver. However, this amount can be increased significantly and renal distribution decreases in patients with impaired renal functions.

Elimination
After intravenous administration of ^{99m}Tc-DMSA is eliminated from the blood with a triphasic pattern in patients with normal renal function.

Half-life
The effective half-life of ^{99m}Tc-DMSA in blood is around 1 hour.

5.3 Preclinical safety data

This product is not intended for regular or continuous administration.
Toxicity with repeated administration of 0.66 mg/kg/day DMSA and 0.23 mg/kg/day of $SnCl_2$ over 14 days in rats was not observed. The dose usually administered to human is 0.14 mg/kg of DMSA.

Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous chloride dihydrate
Ascorbic acid
D-mannitol
Nitrogen

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 – 6 months.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution: 4 hours. Store below 25°C in a suitable radiation lead shield.

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.
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

10 ml 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

General warning
Radiopharmaceuticals should be received, used and administered only by authorised persons in designated clinical settings. Their receipt, storage, use, transfer and disposal are subject to the regulations and/or appropriate licenses 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 medicinal product 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 pertechnetate (^{99m}Tc) is added, adequate shielding of the final preparation must be maintained.

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spill of urine, vomiting 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.
For instructions on extemporary preparation of the medicinal product before administration, see section 12.

7. MARKETING AUTHORISATION HOLDER

Narodowe Centrum Badań Jądrowych
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05-400 Otwock, Poland
Phone: +48 22 7180700
Fax: +48 22 7180350
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8. MARKETING AUTHORISATION NUMBER

Marketing authorisation number: R/3440

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16.05.1989
Date of latest renewal: 27.08.2013

10. DATE REVISION OF THE TEXT

27.04.2017

11. DOSIMETRY

Technetium (^{99m}Tc) is produced by means of a (^{99}Mo/^{99m}Tc) radionuclide generator and decays with the emission of gamma radiation with an 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.

The projected radiation doses to organs and tissues of a patient after intravenous injection of ^{99m}Tc-DMSA are given in the table below.
These data are adopted from ICRP publication 80 (International Commission of Radiological Protection, Radiation Dose to Patients from Radiopharmaceuticals, Pergamon Press, 1998).