2) Patients with high bone uptake and/or severely impaired kidney function

Organ	Absorbed dose per unit administered activity [mGy/MBq]				
	Adults	Children 15 years	Children 10 years	Children 5 years	Children 1 year
Adrenals	0.0035	0.005	0.00072	0.011	0.021
Bladder wall	0.0025	0.0035	0.0054	0.0074	0.015
Bone surfaces	0.12	0.16	0.26	0.43	1.0
Breast	0.0021	0.0021	0.0032	0.0051	0.0096
GI-tract					
Stomach wall	0.0026	0.0032	0.0051	0.0073	0.014
Small intestine	0.0031	0.0038	0.0057	0.0085	0.016
ULI	0.0029	0.0036	0.0053	0.0086	0.015
LLI	0.0034	0.0042	0.0065	0.0096	0.018
Kidneys	0.003	0.0037	0.0056	0.0087	0.016
Liver	0.0027	0.0033	0.0049	0.0075	0.014
Lungs	0.003	0.0037	0.0053	0.0081	0.015
Ovaries	0.0029	0.0041	0.0059	0.0089	0.016
Pancreas	0.0032	0.004	0.0059	0.0089	0.016
Red Marrow	0.018	0.023	0.037	0.072	0.14
Spleen	0.0026	0.0034	0.0051	0.0078	0.015
Testes	0.0023	0.0027	0.0039	0.006	0.011
Thyroid	0.0024	0.0037	0.0054	0.0083	0.014
Uterus	0.0029	0.0037	0.0054	0.0082	0.015
Other tissue	0.003	0.0036	0.0053	0.0081	0.015
Effective dose [mSv/MBq]	**0.0082**	**0.011**	**0.017**	**0.028**	**0.061**

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.

PoltechMDP is designed for labelling with technetium-99m as eluate of sodium pertechnetate-^{99m}Tc obtained from the ^{99}Mo/^{99m}Tc radionuclide generator. The labeling procedure should ensure sterility of the preparation, precautions to minimize radiation exposure by the use of suitable shielding should be taken.

Labelling procedure:
The vial is reconstituted with sodium pertechnetate (^{99m}Tc) solution with activity of 1100 - 18500 MBq.
1. Place the kit vial containing the lyophilisate in an appropriate radioprotective shield.
2. Using a syringe inject (by piercing the rubber stopper) about 5 ml of eluate of sodium pertechnetate-^{99m}Tc (or eluate with desired activity pre-diluted with sterile saline) into the vial.
3. Using the same syringe relieve the excess of pressure in the vial by withdrawing the equivalent volume of gas.
4. 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. Leave the vial for 15 min.
5. The resultant solution is a ready-to-use solution for injection.

^{99m}Tc-MDP preparation should be used within 8 hours after completing the labelling procedure.

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

Radiochemical purity of the preparation should be measured by TLC method before administration to the patient.

Quality control:
Radiochemical purity measurement by Thin Layer Chromatography – two chromatographic systems according to Ph.Eur. current edition, Monograph 0641.

Impurity A
1. ITLC-SG plates (silica gel coated glass-fibre plates)
2. Developing solution: 136 g/l sodium acetate
3. Applying the sample on a plate: apply about 2 µl of the examined solution (with radioactivity from 50 MBq/ml to 200 MBq/ml) about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate
4. Developing: immediately, until the solvent front moves to about 4/5 of the plate
5. Drying: in the air
6. Detection: suitable radiation detector

Under these conditions:
- non-bound, reduced ^{99m}Tc and ^{99m}Tc colloidal forms (**Impurity A**) remain at the origin (R_f= 0.0 - 0.1).
- ^{99m}Tc-MDP complex and free pertechnetate ion $^{99m}TcO_4^-$ migrate with solvent front (R_f = 0.9 - 1.0).

Impurity B
1. ITLC-SG plates (silica gel coated glass-fibre plates)
2. Developing solution: methyl ethyl ketone (MEK)
3. Applying the sample on a plate: apply about 2 µl of the examined solution (with radioactivity from 50 MBq/ml to 200 MBq/ml) about 1.5 cm from the bottom of a 1.5 cm x 12 cm chromatographic plate
4. Developing: immediately, until the solvent front moves about 4/5 of the plate
5. Drying: in the air
6. Detection: suitable radiation detector

Under these conditions:
- free pertechnetate ion $^{99m}TcO_4^-$ (**Impurity B**) migrates with the solvent front (R_f = 0.9 - 1.0).
- ^{99m}Tc-MDP complex and ^{99m}Tc colloidal forms remain at the origin (R_f = 0.0 - 0.1).

Radiochemical purity of ^{99m}Tc-MDP complex: not less than 95% of total technetium-99m.
Calculate the % of radioactivity ^{99m}Tc-MDP complex as:

100 – (A+B)

Where:
A = percentage of Impurity A radioactivity, determined in the test of Impurity A
B = percentage of Impurity B radioactivity, determined in the test of Impurity B

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POLATOM

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

PoltechMDP, 5 mg,

kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 vial contains:
methylenediphosphonic acid 5 mg
as sodium methylenediphosphonate 6.25 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-MDP is intended for skeletal imaging utilizing radioactive properties of technetium-99m and the affinity of methylenediphosphonic acid to hydroxyapatite crystals which form inorganic structure of bone tissue.

4.2 Posology and method of administration
Product intended for intravenous administration.
This radiopharmaceutical may be used only by authorized persons. Safety precautions for careful handling this radiopharmaceutical should be observed.
The radiopharmaceutical ^{99m}Tc-MDP is administered intravenously after labelling with sterile, oxidant-free eluate from a radionuclide generator ^{99}Mo/^{99m}Tc, in accordance with the labelling instructions - see section 12.
For radiolabelling of one vial the 5 ml of sodium pertechnetate (^{99m}Tc) solution with activity of 1100 - 18500 MBq should be used.

Image acquisition
High quality scintigraphy images (e.g. in three phase scintigraphy) are obtained by using the so-called late phase static scintigraphy, i.e. by performing the examination not earlier than 2 hours after intravenous administration of radiopharmaceutical. The earlier acquisition may result in images which only partly reflect the metabolic activity of the bones.

Slow administration of the preparation over a period of around 30 seconds is recommended.

Posology
Adults
The activity recommended for a single examination of skeletal system in adult patient ranges from 370 to 740 MBq, however depending on indications other activities 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 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 40 MBq is necessary in order to obtain images of sufficient quality.

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
If hypersensitivity or anaphylactic reactions occurs, 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.

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 does not require special preparation for examination.
For obtaining the images of sufficient quality it is recommended to urinate before the examination.

The content of the vial is intended for preparation of radiopharmaceutical ^{99m}Tc-MDP and may be administered to the patient only after completion of labelling procedure.
An increased sensitivity of the epiphyses in growing bone on ionising radiation should be considered when making a decision about examination.

An adequate hydration of a patient and frequent voiding are necessary to minimize radiation dose to the bladder.
The exposure to radiation is increased in patients with renal insufficiency. This should be considered in the calculation of the dose to be administered.

Specific warnings
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
An increased extraosseous accumulation of the radiotracer is reported in concomitant administration of iron containing compounds, acute administration of diphosphonate, several cytostatic and immunosuppressive drugs, aluminium-containing antacids, X-ray contrast media, antibiotics, anti-inflammatory substances, injections of calcium gluconate, heparin calcium and γ-amino caproic acid.

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.

Examinations using radiopharmaceuticals in women of childbearing potential should be carried out during the first 10 days following the onset of menses.

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.
Administration of 700 MBq ^{99m}Tc-MDP to a patient with normal bone uptake results in an absorbed dose to the uterus of 4.27 mGy. The dose decreases to 2.03 mGy in patients with high bone uptake and/or severely

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

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

Undesirable effects	Frequency
Congenital and familial/ genetic disorders: hereditary defects	Frequency not known (cannot be estimated from the available data)
Nervous system disorders: headache	Frequency not known (cannot be estimated from the available data)
Gastrointestinal disorders: vomiting	Frequency not known (cannot be estimated from the available data)
Musculoskeletal, connective tissue and bone disorders: arthralgia	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)
Surgical and medical procedures: cutaneous vasodilation	Frequency not known (cannot be estimated from the available data)
Vascular disorders: fall in blood pressure and hypotensive symptoms, nausea	Frequency not known (cannot be estimated from the available data)
General disorders and administration site conditions: hypersensitivity reactions, local rash or generalized rash with itching and dermal irritation, malaise, oedema of the extremities	Frequency not known (cannot be estimated from the available data)
Immune system disorders: Anaphylaxis	Very rare (< 1/10000)

Occasionally (approximately 1 out of 200000 investigations) hypersensitivity reactions, including very rare life-threatening anaphylaxis, may occur following intravenous administration of ^{99m}Tc-MDP. Cases of local rash or generalized rash with itching and dermal irritation have been reported; onset of the reaction is commonly several hours post-injection and it may last up to 48 hours. Treatment with a non-sedative histamine H_1 antagonist is helpful.

Other reactions reported include a fall in blood pressure and hypotensive symptoms, nausea, vomiting, cutaneous vasodilation, headache, malaise, oedema of the extremities and arthralgia.
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.

According to the literature data (J. Nucl. Med., 1996, 37, 185 - 192, 1064 - 1067), the following adverse reactions after the intravenous administration of the radiopharmaceutical ^{99m}Tc-MDP have been reported sporadically: chills, pain at the injection site, fever, nausea, vomiting, flushing, back pain, abdominal pain, headache, dizziness, sweating, hypersensitivity reactions, fatigue, photophobia, erythema, skin rash, pruritus, seizures, metallic taste, cardiac arrest (a single fatal outcome due to secondary cardiac arrhythmia has been reported).

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-MDP 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: V09BA02

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

5.2 Pharmacokinetic properties
In the first 3 minutes after injection of technetium-99m medronate there is soft tissue uptake and renal accumulation.

With increasing clearance from these compartments, progressive accumulation in the skeletal system is seen initially in the lumbar vertebrae and the pelvic region.

Blood clearance proceeds in 3 phases:

1. Rapid phase (t½ = 3.5 min.)
2. Medium phase (t½ = 27 min.)
3. Slow phase (t½ = 144 min.)

The rapid phase represents the transfer of the radioactive substance from the circulation into the extravascular system, the medium phase involving skeletal uptake.

The slow phase is probably associated with the release of the ^{99m}Tc-MDP complex from a protein bound complex. About 50% of the dose injected accumulates in the skeleton.

Maximum bone accumulation is reached 1 hour after injection and remains practically constant up to 72 hours. The circulating unbound complex is eliminated via the kidneys.

The peak of activity through the kidneys is reached after approximately 20 minutes.

Within 1 hour, with normal renal function, around 32% of the total quantity of unbound complex has undergone glomerular filtration, within 2 hours 47.5% and within 6 hours 60%.

The quantity of phosphonate, within the recommended dose range, has no effect on renal excretion.

The quantity eliminated via the intestines is insignificant.
The level of accumulation in the skeletal system depends on the circulation and the extent of regeneration of basic bone material. Whole body retentions of 31.6 ± 5% are reported in healthy individuals, 38.2 ± 7% in those with extensive metastases, and 49 ± 11% in primary hyperparathyroidism and 45% in osteoporosis.

5.3 Preclinical safety data
This product is not intended for regular or continuous administration. Very low toxicity of the complex (LD_{50} = 190 mg/kg) allows safe administration of diagnostic doses. No immunization effects have been observed.

6. PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Stannous chloride dihydrate
Ascorbic acid
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 - 1 year.
After radiolabelling with sodium pertechnetate (^{99m}Tc) solution: 8 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 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 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
ul. Andrzeja Sołtana 7
05-400 Otwock, Poland
Phone: +48227180700
Fax: +48227180350
e-mail: polatom@polatom.pl

8. MARKETING AUTHORISATION NUMBER
Marketing authorisation number: R/3439

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
Date of first authorisation: 28.11.1985
Date of latest renewal: 27.08.2013

10. DATE REVISION OF THE TEXT
30.08.2016

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-MDP (^{99m}Tc – labeled phosphates and phosponates) are given in the table below.

These data are adopted from ICRP 53 and 80 *(International Commission of Radiological Protection)*.

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)

1) Patients with normal bone uptake

Absorbed dose per unit administered activity [mGy/MBq]					
Organ	**Adults**	**Children 15 years**	**Children 10 years**	**Children 5 years**	**Children 1 year**
Adrenals	0.0021	0.0027	0.0039	0.0058	0.011
Bladder wall	0.048	0.06	0.088	0.073	0.13
Bone surfaces	0.063	0.082	0.13	0.22	0.53
Brain	0.0017	0.0021	0.0028	0.0043	0.0061
Breast	0.00071	0.00089	0.0014	0.0022	0.0042
Gall bladder	0.0014	0.0019	0.0035	0.0042	0.0067
Gastrointestinal tract					
Stomach	0.0012	0.0015	0.0025	0.0035	0.0066
Small intestine	0.0023	0.0029	0.0044	0.0053	0.0095
Colon	0.0027	0.0034	0.0053	0.0061	0.011
ULI	0.0019	0.0024	0.0039	0.0051	0.0089
LLI	0.0038	0.0047	0.0072	0.0075	0.013
Heart	0.0012	0.0016	0.0023	0.0034	0.006
Kidneys	0.0073	0.0088	0.012	0.018	0.032
Liver	0.0012	0.0016	0.0025	0.0036	0.0066
Lungs	0.0013	0.0016	0.0024	0.0036	0.0068
Muscles	0.0019	0.0023	0.0034	0.0044	0.0079
Trachea	0.001	0.0013	0.0019	0.003	0.0053
Ovaries	0.0036	0.0046	0.0066	0.007	0.012
Pancreas	0.0016	0.002	0.0031	0.0045	0.082
Bone marrow	0.0092	0.001	0.017	0.033	0.067
Skin	0.001	0.0013	0.002	0.0029	0.0055
Spleen	0.0014	0.0018	0.0028	0.0045	0.0079
Testes	0.0024	0.0033	0.0055	0.0058	0.011
Thymus	0.001	0.0013	0.0019	0.003	0.0053
Thyroid	0.0013	0.0016	0.0023	0.0035	0.0056
Uterus	0.0063	0.0076	0.012	0.011	0.018
Other organs	0.0019	0.0023	0.0034	0.0045	0.0079
Effective dose [mSv/MBq]	**0.0057**	**0.007**	**0.011**	**0.014**	**0.027**

The effective dose equivalent resulting from an administered activity of 740 MBq to a patient of 70 kg body weight is 4.22 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).