Summary of Product Characteristics

1. NAME OF THE MEDICINAL PRODUCT

Nephromag, 0.2 mg, Kit for radiopharmaceutical preparation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The kit contains two different vials: (1) and (2).
Vial (1) contains 0.2 mg of the mercaptoacetyltriglycine (mertiatide).
Vial (2) contains 2.5 mL phosphate buffer solution.

For a full list of excipients, see section 6.1.

The radioisotope is not part of the kit. The kit contains all non radioactive components required for the reconstitution of technetium-(99mTc) mertiatide solution for injection.

3. PHARMACEUTICAL FORM

Kit for radiopharmaceutical preparation.

Properties of the product after labelling:
Clear to slightly opalescent, colourless, aqueous solution.
pH: 7.1-7.5

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.
After reconstitution and labelling with sodium pertechnetate(99mTc) solution, the radiopharmaceutical product obtained, technetium-(99mTc) mertiatide, is used for the evaluation of nephrological and urological disorders in particular for the study of function, morphology and perfusion of the kidneys and characterisation of urinary outflow.

4.2 Posology and method of administration

Adults and elderly
Adults and elderly: 40 - 200 MBq, depending on the pathology to be studied and the method to be used.

Population aged less than 18 years
Although Nephromag may be used in paediatric patients, formal studies have not been performed. Clinical experience indicates that, for paediatric use, the activity should be reduced. Because of the variable relationship between the size and body weight of patients, it is sometimes more satisfactory to adjust activities to body surface area.
A practical approach is to adopt the recommendations of the Paediatric Task Group of the European Association of Nuclear Medicine (EANM). See table below.

Reduction of the radioactivity to less than 10 % of the adult activity would generally result in technically unsatisfactory procedures.

Fraction of adult activity (Paediatric Task Group EANM, 1990).

3 kg = 0.1	22 kg = 0.5	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

Method of administration
Nephromag is administered after reconstitution and labelling.
This medicinal product must be administered exclusively by authorised professional.
The radiopharmaceutical is injected intravenously, see section 4.4 “General warnings”.
The scintigraphic investigation is usually started immediately after administration.

For detailed instructions about the correct preparation of the patient, see section 4.4.

For detailed instructions about the correct administration/use of Nephromag, see section 6.6 and section 12.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Radiopharmaceutical agents should only be used by qualified personnel with the appropriate government authorization for the use and manipulation of radionuclides.

Appropriate means for the treatment of allergic reactions (adrenalin, corticosteroids and antihistamines) should always be kept available for immediate use even if the probability for undesirable effects (see 4.8) to occur is rare.

Small amounts of technetium (99mTc)-labelled impurities may be present and/or are formed during the labelling process. As some of these impurities are distributed to the liver and excreted via the gall bladder they may disturb the late phase (after 30 minutes) of a dynamic renal study due to the overlap of kidney and liver in the region of interest.

If the addition of buffer is missed, this will result in an irritation at the injection site.

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 study in order to reduce radiation.

General warnings
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 regulations and/or appropriate licences of the local competent official organisations.
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, complying with the requirements of Good Manufacturing Practice for pharmaceuticals.

4.5 Interaction with other medicaments and other forms of interaction

Technetium-(99mTc) mertiatide is not known to interfere with agents commonly prescribed to patients requiring the above mentioned investigations (e.g. antihypertensives or medicinal agents used to treat or prevent organ transplant rejection).

4.6 Pregnancy and lactation

There is no clinical experience with the use of technetium-(99mTc) mertiatide in pregnant women. No animal data about embryo toxicity are available.
Before administering a radioactive medicinal product to a woman 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.
Radionuclide procedures carried out on a pregnant woman involve radiation doses to the foetus. Taking into account normal renal function, 200 MBq of technetium-(99mTc) mertiatide administered result in an absorbed uterus dose of 2.4 mGy.
Alternative techniques that do not involve ionising radiation have to be considered.
Technetium-(99mTc) mertiatide must not be administered during pregnancy unless mandatorily necessary. The benefit for the mother has to overweigh the risk for the foetus.
The least radiation exposure possible should be applied to acquire the desired clinical information.
Before administering a radioactive medicinal product to a breast-feeding mother 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, bearing in mind the secretion of activity into breast milk. If the administration is considered necessary breast-feeding should be interrupted for 24 hours and the expressed feeds discarded. Moreover, for radioprotection reasons, the mother is recommended to avoid close contact with the baby during the initial 24 hours following injection. In the event of uncertainty, breastfeeding is usually advised to be restarted when the radioactivity in the milk will not result in a radiation dose to the child greater than 1 mSv.

4.7 Effect on ability to drive and to use machines

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

4.8 Undesirable effects

A very rare mild anaphylactoid reactions have been reported (< 0.01 %), characterised by uriticarial rash, swelling of eyelids and coughing.
Occasionally vasovagal reactions of a mild nature have been reported. A cerebral convulsion in a sedated fifteen days old child has been reported, but causative relation with the administration of the radiopharmaceutical was not proven.

Exposure to ionisation radiation is linked with cancer induction and a potential for development of hereditary defects. For diagnostic nuclear medicine investigations current evidence suggests that these adverse effects might only occur with low frequency because of the low radiation doses incurred.
For most diagnostic nuclear medical procedures, the radiation dose delivered (E) is less than 20 mSv. A worst case calculation for the procedure in question gives values of 2 mSv for an adult and 0.76 mSv for a 1 year old child after injection of 200 and 20 MBq respectively.

4.9 Overdose

The risk of an excessive technetium-(99mTc) mertiatide dose is largely theoretical and most likely to be due to an excessive radiation exposure.
In such circumstances the radiation to the body (kidney, bladder and gall bladder) can be reduced by forced diuresis and frequent bladder voiding.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: radiopharmaceuticals, ATC Code: V09CA03
No pharmaco-dynamic effect is known for technetium-(99mTc) mertiatide at the chemical doses envisaged.
Measuring the counts rate in the kidneys over time allows the evaluation of the renal perfusion, function and urinary outflow.

5.2 Pharmacokinetic properties

After intravenous injection technetium-(99mTc) mertiatide is rapidly cleared from the blood by the kidneys. Technetium-(99mTc) mertiatide binds in a 78-90 % proportion to plasma proteins. In normal renal function 70 % of the administered activity is excreted within 30 min. and more than 95 % within 3 hours. These values are dependent on the pathology of the kidneys and the urogenital system. The mechanism of excretion is predominantly based on tubular secretion. Glomerular filtration accounts for 11 % of total clearance.

5.3. Preclinical safety data

It has been reported that no acute, subacute, subchronic or mutagenic effects have been observed in preclinical studies. However, no detailed information is available for these studies.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

vial (1):
Stannous chloride dihydrate
Disodium (R,R)-tartrate dihydrate
Sodium hydroxide
Hydrochloric acid

vial (2):
Sodium monohydrogenphosphate dihydrate
Sodium dihydrogenphosphate dihydrate
Hydrochloric acid
Water for injections

The vials do not contain a preservative agent.

6.2 Incompatibilities

Not known. However, in order not to compromise the stability of technetium-(99mTc) mertiatide, preparations should not be administered together with other drugs.

6.3 Shelf life

Nephromag expires after 15 months.
The technetium-(99mTc) mertiatide should be injected within 6 hours after preparation.

6.4 Special precautions for storage

Store in a refrigerator at 2 – 8 °C.
Store in the original package in order to protect from light.
The labelled preparation must be stored at 2 – 8 °C for aseptic reasons.
Storage should be in accordance with national regulations for radioactive material.

6.5 Nature and contents of container

Glass vial (10 mL) closed with a butyl rubber stopper and sealed with an aluminium crimpcap. Nephromag is supplied as five vials with powder (active substance: mertiatide) together with five vials with 2.5 mL sterile phosphate buffer solution in one carton.

6.6 Special precautions for disposal

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions should be in accordance with national regulations for radioactive materials.
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

ROTOP Pharmaka AG
Bautzner Landstrasse 45
D-01454 Radeberg
Federal Republic of Germany

Tel.: +49 351 26 95 395
Fax: +49 351 26 95 311
E-Mail: info@rotop-pharmaka.de

8. MARKETING AUTHORIZATION NUMBER

HK-59086

9. DATE OF FIRST AUTHORIZATION/RENEWAL OF THE AUTHORISATION
15/06/2006 / 02/06/2009

10. DATE OF REVISION OF THE TEXT
12/2010

11. DOSIMETRY

Absorbed doses:
Technetium (99mTc) mertiatide (Normal renal function)

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.00039	0.00051	0.00082	0.00120	0.00250
Bladder	0.11000	0.14000	0.17000	0.18000	0.32000
Bone surfaces	0.00130	0.00160	0.00210	0.00240	0.00430
Brain	0.00010	0.00013	0.00022	0.00035	0.00061
Breast	0.00010	0.00014	0.00024	0.00039	0.00082
Gall bladder	0.00057	0.00087	0.00200	0.00170	0.00280
GI-tract					
Stomach	0.00039	0.00049	0.00097	0.00130	0.00250
SI	0.00230	0.00300	0.00420	0.00460	0.00780
Colon	0.00340	0.00430	0.00590	0.00600	0.00980
ULI	0.00170	0.00230	0.00340	0.00400	0.00670
LLI	0.00570	0.00700	0.00920	0.00870	0.01400
Heart	0.00018	0.00024	0.00037	0.00057	0.00120
Kidneys	0.00340	0.00420	0.00590	0.00840	0.01500
Liver	0.00031	0.00043	0.00075	0.00110	0.00210
Lungs	0.00015	0.00021	0.00033	0.00050	0.00100
Muscles	0.00140	0.00170	0.00220	0.00240	0.00410
Oesophagus	0.00013	0.00018	0.00028	0.00044	0.00082
Ovaries	0.00540	0.00690	0.00870	0.00870	0.01400
Pancreas	0.00040	0.00050	0.00093	0.00130	0.00250
Red marrow	0.00093	0.00120	0.00160	0.00150	0.00210
Skin	0.00046	0.00057	0.00083	0.00097	0.00180
Spleen	0.00036	0.00049	0.00079	0.00120	0.00230
Testes	0.00370	0.00530	0.00810	0.00870	0.01600
Thymus	0.00013	0.00018	0.00028	0.00044	0.00082
Thyroid	0.00013	0.00016	0.00027	0.00044	0.00082
Uterus	0.01200	0.01400	0.01900	0.01900	0.03100
Remaining organs	0.00130	0.00160	0.00210	0.00220	0.00360
Effective dose (mSv/MBq)	**0.00700**	**0.00900**	**0.01200**	**0.01200**	**0.02200**

Bladder wall contributes up to 80% of the effective dose.
Effective dose if the bladder is emptied 1 or 0.5 hours after administration:

1 hour	0.00250	0.00310	0.00450	0.00640	0.00640
30 min	0.00170	0.00210	0.00290	0.00390	0.00680

Absorbed doses:
Technetium (99mTc) mertiatide (Abnormal renal function)

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.00160	0.00210	0.00320	0.00480	0.00860
Bladder	0.08300	0.11000	0.13000	0.13000	0.23000
Bone surfaces	0.00220	0.00270	0.00380	0.00500	0.00910
Brain	0.00061	0.00077	0.00130	0.00200	0.00360
Breast	0.00054	0.00070	0.00110	0.00170	0.00320
Gall bladder	0.00160	0.00220	0.00380	0.00460	0.00640
GI-tract					
Stomach	0.00120	0.00150	0.00260	0.00350	0.00610
SI	0.00270	0.00350	0.00500	0.00600	0.01000
Colon	0.00350	0.00440	0.00610	0.00690	0.01100
ULI	0.00220	0.00300	0.00430	0.00560	0.00930
LLI	0.00510	0.00630	0.00850	0.00860	0.01400
Heart	0.00091	0.00120	0.00180	0.00270	0.00480
Kidneys	0.01400	0.01700	0.02400	0.03400	0.05900
Liver	0.00140	0.00180	0.00270	0.00380	0.00660
Lungs	0.00079	0.00110	0.00160	0.00240	0.00450
Muscles	0.00170	0.00210	0.00290	0.00360	0.00640
Oesophagus	0.00074	0.00097	0.00150	0.00230	0.00410
Ovaries	0.00490	0.00630	0.00810	0.00870	0.01400
Pancreas	0.00150	0.00190	0.00290	0.00430	0.00740
Red marrow	0.00150	0.00190	0.26000	0.00310	0.00500
Skin	0.00078	0.00096	0.00150	0.00200	0.00380
Spleen	0.00150	0.00190	0.00290	0.00430	0.00740
Testes	0.00340	0.00470	0.00710	0.00780	0.01400
Thymus	0.00074	0.00097	0.00150	0.00230	0.00410
Thyroid	0.00073	0.00095	0.00150	0.00240	0.00440
Uterus	0.01000	0.01200	0.01600	0.01600	0.02700
Remaining organs	0.00170	0.00210	0.00280	0.00340	0.00600
Effective dose (mSv/MBq)	**0.00610**	**0.00780**	**0.01000**	**0.01100**	**0.19000**

Absorbed doses:
Technetium (99mTc) mertiatide (Acute unilateral renal blockage)

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	0.01100	0.01400	0.02200	0.03200	0.05500
Bladder	0.05600	0.07100	0.09100	0.09300	0.17000
Bone surfaces	0.00310	0.00400	0.00580	0.00840	0.01700
Brain	0.00011	0.00014	0.00023	0.00039	0.00075
Breast	0.00038	0.00051	0.00100	0.00160	0.00300
Gall bladder	0.00620	0.00730	0.01000	0.01600	0.02300
GI-tract					
Stomach	0.00390	0.00440	0.00700	0.00930	0.01200
SI	0.00430	0.00550	0.00850	0.01200	0.01900
Colon	0.00390	0.00500	0.00720	0.00920	0.00150
ULI	0.00400	0.00510	0.00760	0.01000	0.01600
LLI	0.00380	0.00480	0.00670	0.00820	0.01300
Heart	0.00130	0.00160	0.00270	0.00400	0.00610
Kidneys	0.20000	0.24000	0.33000	0.47000	0.81000
Liver	0.00440	0.00540	0.00810	0.01100	0.01700
Lungs	0.00110	0.00160	0.00250	0.00390	0.00720
Muscles	0.00220	0.00270	0.00370	0.00510	0.00890
Oesophagus	0.00038	0.00054	0.00085	0.00150	0.00230
Ovaries	0.00380	0.00510	0.00710	0.00920	0.01500
Pancreas	0.00740	0.00900	0.01300	0.01800	0.02900
Red marrow	0.00300	0.00360	0.00500	0.00600	0.00830
Skin	0.00082	0.00100	0.00150	0.00220	0.00420
Spleen	0.00980	0.01200	0.01800	0.02600	0.04000
Testes	0.00200	0.00290	0.00450	0.00500	0.00980
Thymus	0.00038	0.00054	0.00085	0.00150	0.00230
Thyroid	0.00017	0.00023	0.00045	0.00092	0.00160
Uterus	0.00720	0.00870	0.01200	0.01300	0.02200
Remaining organs	0.00210	0.00260	0.00360	0.00470	0.00800
Effective dose (mSv/MBq)	**0.01000**	**0.01200**	**0.01700**	**0.02200**	**0.03800**

11.1 Nuclear physical properties
Technetium-(99mTc) is obtained from a (99Mo)/(99mTc) sterile generator and decays by gamma emission (gamma energy 140/142 keV) with a physical half-life of 6.02 hours to technetium-(99Tc), which decays to stable ruthenium-(99Ru).
Technetium-(99Tc) may be considered stable due to its long half-life of 214,000 years.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS
12.1 Instructions for use/handling
The content of vial (1) is labelled with sodium pertechnetate (99mTc) solution at room temperature. The labelling reaction is stopped after 15 minutes by adding the buffer solution.
Labelling should be done using an eluate with a radioactive concentration between 40 and 1250 MBq/mL. Only eluates obtained from a generator, which has been eluted once in the preceding 24 hours, should be used. Dilution of the preparation should be done with saline.

12.2 Instruction for labelling
The radiopharmaceutical is prepared according to the following labelling instructions immediately before use:
The labelling procedure has to be carried out under aseptic conditions.
Place vial (1) into an adequate lead shielding. Swab the rubber septum with an appropriate disinfectant and let it dry.
Inject 2 mL of sodium pertechnetate (99mTc) solution into vial (1) using a syringe. Then withdraw the same volume of nitrogen from the vial with the same syringe for pressure compensation.
Shake the vial carefully in order to moisten. The complete content of the vial is for complete dissolution of any powder.
After 15 minutes reaction time transfer a volume of 2 mL buffer solution from vial (2) into vial (1) using a new syringe. Then withdraw the same volume of nitrogen from the vial with the same syringe for pressure compensation.
Shake carefully for good mixing. Determine the total radioactivity and calculate the volume to be injected.
If necessary, dilute with sterile isotonic saline up to a final total volume of 10 mL. Shake again for good mixing.

Properties of the product after labelling:
Clear to slightly opalescent, colourless, aqueous solution.
pH: 7.1-7.5

12.3 Instructions for quality control
The following methods may be used:

<u>HPLC method</u>
The radiochemical purity of the labelled substance is examined by high performance liquid chromatography (HPLC) using a suitable detector of radioactivity, on a 25 cm RP18 column, flow rate 1.0 mL/min. Mobile phase A is a 93:7 mixture of phosphate solution (1.36 g KH_2PO_4, adjusted with 0.1 M NaOH to pH 6) and ethanol. Mobile phase B is a 1:9 mixture of water and methanol.

Use a gradient elution program with the following parameters:

Time (min):	Flow (mL/min):	% A	% B
15	1	100	0
5	1	0	100
5	2	100	0

The technetium-(99mTc) mertiatide peak appears at the end of the passage of mobile phase A.

The injection volume is 5 µl and the total count rate per channel must not exceed 30.000.

Requirement:

	t = 0	after 6 hours
technetium-(99mTc) mertiatide	≥ 94 %	≥ 94 %
hydrophilic impurities	≤ 3.0 %	≤ 3.0 %
lipophilic impurities	≤ 4.0 %	≤ 4.0 %

<u>Simplified rapid procedure</u>
This method is based on cartridges, which are widely used as sample pre-treatment of aqueous solutions for chromatography. The cartridge (e.g. Sep-Pak Plus C 18, Waters) is washed with 10 mL absolute ethanol, followed by 10 mL 0.001 M hydrochloric acid. Remaining residues of the solutions are removed by 5 mL of air.
0.05 mL technetium-(99mTc) mertiatide solution is applied on the cartridge. Elute with 10 mL of 0.001 M hydrochloric acid and collect this first eluate (hydrophilic impurities). Elute the cartridge with ethanol/ 9 g/L sodium chloride solution in a ratio of 1:1. This second eluate contains technetium-(99mTc) mertiatide. The cartridge contains the lipophilic impurities.
Measure the radioactivity of each portion. Sum up the radioactivity of the eluates and the cartridge as 100 % and calculate the respective percentages.

Be aware to elute slowly (drop wise).

Requirement: technetium-(99mTc) mertiatide ≥ 94 %

12.4 Waste
Any unused product or waste material should be disposed of in accordance with local requirements.