SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

TechneScan® MAG3
(Curium Netherlands catalogue number: DRN 4334)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains:
Betiatide 1 mg

To be used with sodium pertechnetate (^{99m}Tc) for the preparation of the diagnostic agent: Technetium (^{99m}Tc) tiatide.

3 PRODUCT DESCRIPTION

Off-white to slightly yellow pellets or powder

4 PHARMACEUTICAL FORM

Powder for solution for injection.

5 CLINICAL PARTICULARS

5.1 Indications

After reconstitution and labelling with sodium pertechnetate (^{99m}Tc) solution the diagnostic agent technetium (^{99m}Tc) tiatide may be used for the evaluation of nephrological and urological disorders in particular for the study of morphology, perfusion, function of the kidney and characterisation of urinary outflow.

5.2 Posology and method of administration

Adults and the elderly : 37-185 MBq (1-5 mCi), depending on the pathology to be studied and the method to be used. Studies of renal blood flow or transport through the ureters generally require a larger dose than studies of intra-renal transport, whereas renography requires smaller activities than sequential scintigraphy.

Children:
Although TechneScan MAG3 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.

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

Activities in children. Fraction of adult activity (Paediatric Task Group EANM, 1990).		
3 kg = 0.10	22 kg = 0.50	42 kg = 0.78
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

Reduction of the amount of radioactivity to less than 10% of the dose for adults will generally result in technically unsatisfactory procedures. In general, the risks are likely to relate to the level of radiation, as the chemical doses are quite small (about 0.2 mg for 185 MBq).

The administration of a diuretic or an ACE inhibitor during the diagnostic procedure is sometimes used for differential diagnosis of nephrological and urological disorders. The scintigraphic investigation is usually performed immediately after administration.

5.3 Contraindications

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

5.4 Special warnings and special precautions for use

5.4.1 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.

5.4.2 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.

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

5.4.4 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.

5.4.5 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.

5.4.6 The agent is not suited for exact monitoring of effective renal plasma flow respectively blood flow in patients with seriously impaired renal function.

5.4.7 Small amounts of ^{99m}Tc-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 influence the late phase (after 30 minutes) of a dynamic renal study due to the overlap of kidney and liver in the region of interest.

5.5 Interaction with other medicaments and other forms of interaction

Technetium (^{99m}Tc) tiatide has not been described to interfere with agents commonly prescribed to or given to patients requiring investigations with Technetium (^{99m}Tc) tiatide (e.g. antihypertensives and medicinal agents used to treat or prevent organ transplant rejection). However, the single administration of a diuretic or ACE inhibitor is sometimes used in the differential diagnosis of nephrological and urological disorders. Administered contrast media may impair tubular renal excretion and thereby influence the technetium (^{99m}Tc) tiatide clearance.

5.6 Pregnancy and lactation

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.

Radionuclide procedures carried out on pregnant women also involve radiation doses to the fetus. Only imperative investigations should be carried out during pregnancy, when likely benefit exceeds the risks incurred by mother and fetus.

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, bearing in mind the secretion of activity in breast milk. If the administration is considered necessary, breast-feeding should be interrupted for 8 hours and the expressed feeds discarded. In the event of uncertainty it is usually advised that breast-feeding can be restarted when the level in the milk will not result in a radiation dose to a child greater than 1 mSv.

5.7 Effects on the ability to drive and use machines

Have not been described.

5.8 Undesirable effects

A few mild anaphylactoid reactions have been reported, characterised by urticarial rash, swelling of eyelids and coughing. Although the probability of the occurrence of such reactions is small, the appropriate treatment of allergic reactions (adrenaline, corticosteroids and antihistamines) should always be kept available for immediate use. Occasionally vasovagal reactions of a mild nature have been reported.

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. 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 effects will occur with low frequency because of the low radiation doses incurred. For most diagnostic investigations using nuclear medicine procedures the radiation dose delivered (Effective Dose Equivalent) is less than 20 mSv. Higher doses might be justified in some clinical circumstances.

5.9 Overdose

The risk of an excessive technetium (^{99m}Tc) tiatide dose is largely theoretical

and most likely to be due to 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.

6 PHARMACOLOGICAL PROPERTIES

6.1 Pharmacodynamic properties

At the chemical doses envisaged technetium (^{99m}Tc) tiatide Injection has no known pharmacodynamic action.

Measuring the activity over the kidneys allows renal blood flow, intrarenal tubular transit times and excretion via the outflow tracts to be recorded separately for both kidneys.

6.2 Pharmacokinetic properties

After intravenous injection technetium (^{99m}Tc) tiatide is rapidly cleared from the blood by the kidneys.

Technetium (^{99m}Tc) tiatide has a relatively high binding to plasma proteins. In normal renal function 70% of the administered dose has been excreted after 30 min. and more than 95% after 3 hours. These latter percentages 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.

6.3 Preclinical safety data

Acute, subacute (8 days) and chronic (13 weeks) toxicity studies as well as mutagenicity studies were performed. At the studied dose levels, up to 1000 times the maximal human dose, no toxicological effects were observed. Similarly, mutagenic effects have not been observed.

6.4 Radiation dosimetry

Estimated absorbed dose (according to the MIRD method)

		mGy/MBq
Bladder wall	Bladder void 2h	0.057
	Bladder void 4.8h	0.127
Gall bladder wall		0.043
Kidneys		0.017
Upper large intestine		0.010
Lower large intestine		0.009
Small intestine		0.007
Liver		0.005
Ovaries	Bladder void 2h	0.003
	Bladder void 4.8h	0.007
Testes	Bladder void 2h	0.002
	Bladder void 4.8h	0.004
Bone marrow	Bladder void 2h	0.002
	Bladder void 4.8h	0.003
Skeleton	Bladder void 2h	0.001
Lungs		0.001
Effective Dose Equivalent (EDE)		0.011 mSv/MBq

The effective dose equivalent after a dose of 185 MBq for a 70kg individual would be

2.0 mSv when the bladder is voided 2 hours after administration.

Although no comparative dosimetric studies have been performed in patients, it is anticipated that the EDE will be lower in patients with renal insufficiency/failure than those with normal renal function. This relates to the contribution of urinary bladder to overall tissue exposure.

7 PHARMACEUTICAL PARTICULARS

7.1 List of excipients

Disodium tartrate
Tin(II)chloride
Hydrochloric acid

7.2 Incompatibilities

Major incompatibilities: not known. However, in order not to compromise the stability of ^{99m}Tc-tiatide, preparations should not be administered together with other drugs.

7.3 Shelf life

12 months.
After labelling Technetium (99mTc) tiatide Injection expires 8 hours after labelling, when stored at room temperature (25 °C).

7.4 Special precautions for storage

TechneScan® MAG3 is to be stored at 2-8 °C.

For storage conditions after radiolabelling of the medicinal product, see section 7.3. Storage should be in accordance with national regulations for radioactive materials.

7.5 Nature and contents of container.

10 ml Type 1 Ph.Eur glass vial closed with a butyl rubber stopper Ph.Eur and sealed with an aluminium crimpcap. TechneScan® MAG3 is supplied as five vials in a carton.

7.6 Instructions for preparation of radiopharmaceuticals

7.6.1 Instruction for labelling

The contents of the vial is to be labelled with Sodium Pertechnetate (^{99m}Tc) Injection Ph.Eur. After reconstitution with a sodium pertechnetate (^{99m}Tc) solution the diagnostic agent technetium (^{99m}Tc) tiatide is obtained upon heating. Only eluates obtained from a ^{99m}Tc -generator, which has been eluted within the preceding 24 hours should be used.Dilution of the preparation should be done with saline. After reconstitution and labelling the solution may be used for one or more administrations.

For labelling it is recommended to use an eluate with the highest possible radioactive concentration, as the formation of labelled impurities is the least when using an eluate with the smallest possible volume.

Elute a 99mTc generator in a 5 ml volume, according to the fractionated elution technique and follow the directions for use for the generator. Use 3 ml eluate.

The desired amount of ^{99m}Tc, with a maximum of 2960 MBq (80 mCi) must be diluted to a volume of 10 ml with saline solution (0.9%). Add this volume to a vial of TechneScan® MAG3. For this a thin needle must be used (G20 or higher)

so that the puncture hole closes again. This prevents the water from entering the vial during the heating and cooling steps that follow.

Heat immediately during 10 minutes in a dry heating device or boiling water bath. During heating the vial should be standing upright in order to prevent traces of metal coming off the rubber stopper, so influencing the labelling procedure unfavourably.

Cool down the vial to room temperature in cold water. The preparation is ready for administration. This ^{99m}Tc labelled preparation can be used until eight hours after completion of the heating step.

Preferably use eluates obtained by fractionated elution. Follow the pertinent directions for use of the generator.

7.6.2 Precaution during the labelling procedure

To indicate that during the heating and the cooling step no contamination of the contents of the vial has occurred, the user is advised to add a suitable dyestuff to the heating bath and to the cooling bath (e.g. methylene blue to make a concentration of 1 % or sodium fluorescein to make a concentration of 0.1 %). The radiolabelled product vial should be examined for contamination (taking appropriate radiological protective measures) prior to use.

7.6.3 Instructions for quality control

The following methods may be used:

1 HPLC method:

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 19 : 1 mixture of phosphate solution (1000 parts 0.01 M NaH_2PO_4 and 114 parts 0.01 M Na_2HPO_4, adjusted 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
10	1	100	0
7	1	0	100
4	2	100	0

The tiatide peak appears at the end of the passage of mobile phase A.
The injection volume is 20 µl and the total count rate per channel must not exceed 30.000.

Requirement:

	t=0	after 8 hours
Tiatide	≥ 95.0%	≥ 94.0%
Total front fractions	≤ 3.0%	≤ 3.0%
Methanol fraction	≤ 4.0%	≤ 4.0%

2 Simplified rapid procedure.

This method may be used as an alternative for the above mentioned methods. The purpose of this method is to check the labelling procedure, as performed by the user in the hospital.

The method is based on cartridges, which are widely used as sample pretreatment of aqueous solutions for chromatography. The cartridge (e.g. Sep-Pak light C18) is washed with 5 ml absolute ethanol, followed by 5 ml 0.001M hydrochloric acid. Remaining residues of the solutions are removed by 5 ml of air.

The Technetium (^{99m}Tc) tiatide solution (e.g. 0.1-0.3 ml, 7.4 MBq or 200 µC) is applied on the cartridge. It is important that the column is not dried out during all the different steps. Elute with 5 ml 0.001 M HCl and collect the eluate. Elute with 5 ml of a phosphate buffer (0.01 M, pH=6.0) containing 0.5% ethanol. Elute the cartridge with 5 ml ethanol - 0.9% sodium chloride solution (50:50). This second eluate contains Technetium (^{99m}Tc) tiatide. The cartridge contains the lipophilic impurities.

Measure the radioactivity and calculate the respective percentages. Use the combined eluted radioactivity as 100%.

Requirement: Technetium (^{99m}Tc) tiatide: not less than 94 %.

8 MANUFACTURED AND RELEASED BY:

Curium Netherlands B.V.
Westerduinweg 3
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The Netherlands

9 INFORMATION OF PRODUCT REGISTRATION HOLDER

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10 MARKETING AUTHORIZATION NUMBER

MAL19984362AZ

11 DATE OF REVISION OF PI

1 April 2024