Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

TechneScan MAG3, powder for solution for injection

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.

The radionuclide is not part of the kit.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder for solution for injection. Kit for radiopharmaceutical preparation.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

This medicinal product is for diagnostic use only.

After radiolabelling with sodium pertechnetate (^{99m}Tc) the solution obtained is used for diagnostic evaluation of renal function.

4.2 Posology and method of administration

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.

Newborn (5kg)	1 year old (10.5 kg)	5 years old (19.5 kg)	10 year old (33 kg)	15 years old (64.5 kg)	Adult (70 kg)
15 MBq	15 MBq	28 MBq	47 MBq	91 MBq	100 MBq

Other activities may be justifiable.

Method of administration
This medicinal product should be reconstituted before administration to the patient. For instructions on extemporary preparation of the medicinal product before administration, see section 12.

For patient preparation, see section 4.4

4.3 Contraindications

Hypersensitivity to the active substance, to any of the excipients listed in section 6.1 or to any of the components of the labelled radiopharmaceutical.

4.4 Special warnings and precautions for use

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.

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.

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.

Paediatric population
For information on the use in paediatric population, see sections 4.2.
These agents should only be used in patients below the age of 18 years if considered essential by the physician.

Specific warnings
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.

Elective procedure with radiopharmaceuticals should only be carried out during the first 10 days following onset of menses.
The product is not suitable for quantitative determination of effective renal blood flow or effective renal plasma flow.

This medicinal product contains less than 1 mmol sodium (23 mg) per dose, i.e. essentially 'sodium- free'.

4.5 Interaction with other medicinal products and other forms of interactions

None known.

Technetium, (^{99m}Tc)tiatide has not been described to interfere with agents commonly prescribed to or given to patients requiring the above mentioned investigations with Technetium (^{99m}Tc)tiatide (e.g. antihypertensive and medicinal agents used to treat or prevent organ transplant rejection).

4.6 Fertility, pregnancy and lactation

^{99m}Tc (as free pertechnetate) has been shown to cross the placental barrier.

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. 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 be carried out during pregnancy when likely benefit exceeds the risk incurred by mother and foetus.

Breast-feeding
Before administering a radioactive medicinal product to a mother who is breast-feeding consideration should be given to the possibility of delaying the administration of radionuclide until the mother has ceased breastfeeding and to 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 8 hours and the expressed feeds discarded.

4.7 Effects on ability to drive and use machines

Technescan MAG3 has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

In single cases anaphylactic or pseudo-allergic reactions may occur after the use of Technescan® MAG3. Such reactions may involve e.g. flushing, skin rashes, headache, nausea and vomiting, dyspnoea, face oedema, pain, or various types of subjective discomfort. Also vasovagal episodes and local reactions at the injection site have been reported. Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. As the effective dose is 0.7 mSv when the maximal recommended activity of 100 MBq is administered these adverse reactions are expected to occur with a low probability.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; e-mail: medsafety@hpra.ie.

4.9 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.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Renal system. Technetium (^{99m}Tc) compounds. ATC code: V 09 CA 03

None stated.

5.2 Pharmacokinetic properties

After intravenous injection tiatide is rapidly cleared from the blood by the kidneys. On the basis of the pharmacokinetic properties tiatide is used as a diagnostic agent in the evaluation of renal blood flow, renal tubular transit and renal excretion for each or both kidneys.

5.3 Preclinical safety data

None stated.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium tartrate dihydrate.
Stannous chloride dihydrate.
Hydrochloric acid

Properties of the medicinal product after labelling:

Clear to slightly opalescent, colourless, aqueous solution
pH : 5.0 – 6.0
Osmolality : slightly hypertonic.

6.2 Incompatibilities

In the absence of compatibility studies this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

12 months.
After radiolabelling 8 hours.
When stored below 25°C.

6.4 Special precautions for storage

Store at 2-8°C (in a refrigerator).

For storage conditions after radiolabelling of the medicinal product, see section 6.3.

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

6.5 Nature and contents of container

10 ml Type I Ph. Eur. glass vial closed with a bromobutyl rubber stopper Ph. Eur. and sealed with an aluminium crimpcap.
Technescan MAG3 is supplied as five vials in a carton.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

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 Technetium (^{99m}Tc) tiatide and are not to be administered directly to the patient without first undergoing the preparative procedure.

For instructions on extemporary preparation of the medicinal product before administration, see section 12.

If at any time in the preparation of this product the integrity of this vial is compromised it should not be used.

Administration procedures should be carried out in a way to minimise risk of contamination of the medicinal product and irradiation of the operators. Adequate shielding is mandatory. The content of the kit before extemporary preparation is not radioactive. However, after sodium pertechnetate (^{99m}Tc), Ph. Eur. is added, adequate shielding of the final preparation must be maintained.

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

7 MARKETING AUTHORISATION HOLDER

Curium Netherlands B.V.
Westerduinweg 3
1755 ZG Petten
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA0690/018/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 2nd March 1992

Date of last renewal: 2nd March 2007

10 DATE OF REVISION OF THE TEXT

November 2021

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 an energy of 140 keV and a half-life of 6 hours to (^{99}Tc) Technetium which, in view of its long half-life of 2.13 x 10^5 years, can be regarded as quasi stable.

The data are given in ICRP publication 80 in 1998.

The following assumptions have been made in this model:
- In the normal case following intravenous administration of MAG3, the substance is rapidly distributed in the extracellular fluid and excreted entirely by the renal system according to the kidney-bladder model. Total body retention is described by a three-exponential function. The renal transit time is assumed to be 4 minutes as for Hippuran.
- When renal function is bilaterally impaired, it is assumed that the clearance rate of the substance is one tenth of that of the normal case, that the renal transit time is increased to 20 minutes, and that a fraction of 0.04 is taken up in the liver. As an example of acute unilateral renal blockage, it is assumed that a fraction of 0.5 of the administered radiopharmaceutical is taken up by one kidney and slowly released to the blood with a half-time of 5 days and subsequently excreted by the other kidney, which is assumed to function normally.

Normal renal function:
Absorbed doses ^{99m}Tc MAG3, ^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	3.9E-04	5.1E-04	8.2E-04	1.2E-03	2.5E-03
Bladder	1.1E-01	1.4E-01	1.7E-01	1.8E-01	3.2E-01
Bone surfaces	1.3E-03	1.6E-03	2.1E-03	2.4E-03	4.3E-03
Brain	1.0E-04	1.3E-04	2.2E-04	3.5E-04	6.1E-04
Breast	1.0E-04	1.4E-04	2.4E-04	3.9E-04	8.2E-04
Gall bladder	5.7E-04	8.7E-04	2.0E-03	1.7E-03	2.8E-03
GI-tract					
Stomach	3.9E-04	4.9E-04	9.7E-04	1.3E-03	2.5E-03
SI	2.3E-03	3.0E-03	4.2E-03	4.6E-03	7.8E-03
Colon	3.4E-03	4.3E-03	5.9E-03	6.0E-03	9.8E-03
ULI	1.7E-03	2.3E-03	3.4E-03	4.0E-03	6.7E-03)
LLI	5.7E-03	7.0E-03	9.2E-03	8.7E-03	1.4E-02)
Heart	1.8E-04	2.4E-04	3.7E-04	5.7E-04	1.2E-03
Kidneys	3.4E-03	4.2E-03	5.9E-03	8.4E-03	1.5E-02
Liver	3.1E-04	4.3E-04	7.5E-04	1.1E-03	2.1E-03
Lungs	1.5E-04	2.1E-04	3.3E-04	5.0E-04	1.0E-03
Muscles	1.4E-03	1.7E-03	2.2E-03	2.4E-03	4.1E-03
Oesophagus	1.3E-04	1.8E-04	2.8E-04	4.4E-04	8.2E-04
Ovaries	5.4E-03	6.9E-03	8.7E-03	8.7E-03	1.4E-02
Pancreas	4.0E-04	5.0E-04	9.3E-04	1.3E-03	2.5E-03
Red marrow	9.3E-04	1.2E-03	1.6E-03	1.5E-03	2.1E-03
Skin	4.6E-04	5.7E-04	8.3E-04	9.7E-04	1.8E-03

Spleen	3.6E-04	4.9E-04	7.9E-04	1.2E-03	2.3E-03
Testes	3.7E-03	5.3E-03	8.1E-03	8.7E-03	1.6E-02
Thymus	1.3E-04	1.8E-04	2.8E-04	4.4E-04	8.2E-04
Thyroid	1.3E-04	1.6E-04	2.7E-04	4.4E-04	8.2E-04
Uterus	1.2E-02	1.4E-02	1.9E-02	1.9E-02	3.1E-02
Remaining Organs	1.3E-03	1.6E-03	2.1E-03	2.2E-03	3.6E-03
Effective dose (mSv/MBq)	**7.0E-03**	**9.0E-03**	**1.2E-02**	**1.2E-02**	**2.2E-02**
The bladder wall contributes up to 80 % of the effective dose. Effective dose if bladder is emptied 1 or 0,5 hours after administration:					
1 hour 30 min.	2.5E-03 1.7E-03	3.1E-03 2.1E-03	4.5E-03 2.9E-03	6.4E-03 3.9E-03	6.4E-03 6.8E-03
For an administered activity of 100 MBq (Maximal dose) the effective dose is 0.7 mSv. The absorbed dose in the target organ (kidney) is 0.34 mSv and the typical radiation dose to the critical organ (bladder wall) is 11 mSv.					

Abnormal renal function:
Absorbed doses ^{99m}Tc MAG3, ^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	1.6E-03	2.1E-03	3.2E-03	4.8E-03	8.6E-03
Bladder	8.3E-02	1.1E-01	1.3E-01	1.3E-01	2.3E-01
Bone surfaces	2.2E-03	2.7E-03	3.8E-03	5.0E-03	9.1E-03
Brain	6.1E-04	7.7E-04	1.3E-03	2.0E-03	3.6E-03
Breast	5.4E-04	7.0E-04	1.1E-03	1.7E-03	3.2E-03
Gall bladder	1.6E-03	2.2E-03	3.8E-03	4.6E-03	6.4E-03
GI-tract					
Stomach	1.2E-03	1.5E-03	2.6E-03	3.5E-03	6.1E-03
SI	2.7E-03	3.5E-03	5.0E-03	6.0E-03	1.0E-02
Colon	3.5E-03	4.4E-03	6.1E-03	6.9E-03	1.1E-02
ULI	2.2E-03	3.0E-03	4.3E-03	5.6E-03	9.3E-03)
LLI	5.1E-03	6.3E-03	8.5E-03	8.6E-03	1.4E-02)
Heart	9.1E-04	1.2E-03	1.8E-03	2.7E-03	4.8E-03
Kidneys	1.4E-02	1.7E-02	2.4E-02	3.4E-02	5.9E-02
Liver	1.4E-03	1.8E-03	2.7E-03	3.8E-03	6.6E-03
Lungs	7.9E-04	1.1E-03	1.6E-03	2.4E-03	4.5E-03
Muscles	1.7E-03	2.1E-03	2.9E-03	3.6E-03	6.4E-03
Oesophagus	7.4E-04	9.7E-04	1.5E-03	2.3E-03	4.1E-03
Ovaries	4.9E-03	6.3E-03	8.1E-03	8.7E-03	1.4E-02
Pancreas	1.5E-03	1.9E-03	2.9E-03	4.3E-03	7.4E-03
Red marrow	1.5E-03	1.9E-03	2.6E-03	3.1E-03	5.0E-03
Skin	7.8E-04	9.6E-04	1.5E-03	2.0E-03	3.8E-03
Spleen	1.5E-03	1.9E-03	2.9E-03	4.3E-03	7.4E-03
Testes	3.4E-03	4.7E-03	7.1E-03	7.8E-03	1.4E-02
Thymus	7.4E-04	9.7E-04	1.5E-03	2.3E-03	4.1E-03

Thyroid	7.3E-04	9.5E-04	1.5E-03	2.4E-03	4.4E-03
Uterus	1.0E-02	1.2E-02	1.6E-02	1.6E-02	2.7E-02
Remaining Organs	1.7E-03	2.1E-03	2.8E-03	3.4E-03	6.0E-03
Effective dose (mSv/MBq)	**6.1E-03**	**7.8E-03**	**1.0E-02**	**1.1E-02**	**1.9E-02**
For an administered activity of 100 MBq (Maximal dose) the effective dose is 0.61 mSv. The absorbed dose in the target organ (kidney) is 1.4 mGy and the typical radiation dose to the critical organ (bladder wall) is 8.3 mGy.					

Acute unilateral renal function:
Absorbed doses ^{99m}Tc MAG3, ^{99m}Tc 6.02 h

	Absorbed dose per unit activity administered (mGy/MBq)				
Organ	Adult	15 years	10 years	5 years	1 year
Adrenals	1.1E-02	1.4E-02	2.2E-02	3.2E-02	5.5E-02
Bladder	5.6E-02	7.1E-02	9.1E-02	9.3E-02	1.7E-01
Bone surfaces	3.1E-03	4.0E-03	5.8E-03	8.4E-03	1.7E-02
Brain	1.1E-04	1.4E-04	2.3E-04	3.9E-04	7.5E-04
Breast	3.8E-04	5.1E-04	1.0E-03	1.6E-03	3.0E-03
Gall bladder	6.2E-03	7.3E-03	1.0E-02	1.6E-02	2.3E-02
GI-tract					
Stomach	3.9E-03	4.4E-03	7.0E-03	9.3E-03	1.2E-02
SI	4.3E-03	5.5E-03	8.5E-03	1.2E-02	1.9E-02
Colon	3.9E-03	5.0E-03	7.2E-03	9.2E-03	1.5E-03
ULI	4.0E-03	5.1E-03	7.6E-03	1.0E-02	1.6E-02)
LLI	3.8E-03	4.8E-03	6.7E-03	8.2E-03	1.3E-02)
Heart	1.3E-03	1.6E-03	2.7E-03	4.0E-03	6.1E-03
Kidneys	2.0E-01	2.4E-01	3.3E-01	4.7E-01	8.1E-01
Liver	4.4E-03	5.4E-03	8.1E-03	1.1E-02	1.7E-02
Lungs	1.1E-03	1.6E-03	2.5E-03	3.9E-03	7.2E-03
Muscles	2.2E-03	2.7E-03	3.7E-03	5.1E-03	8.9E-03
Oesophagus	3.8E-04	5.4E-04	8.5E-04	1.5E-03	2.3E-03
Ovaries	3.8E-03	5.1E-03	7.1E-03	9.2E-03	1.5E-02
Pancreas	7.4E-03	9.0E-03	1.3E-02	1.8E-02	2.9E-02
Red marrow	3.0E-03	3.6E-03	5.0E-03	6.0E-03	8.3E-03
Skin	8.2E-04	1.0E-03	1.5E-03	2.2E-03	4.2E-03
Spleen	9.8E-03	1.2E-02	1.8E-02	2.6E-02	4.0E-02
Testes	2.0E-03	2.9E-03	4.5E-03	5.0E-03	9.8E-03
Thymus	3.8E-04	5.4E-04	8.5E-04	1.5E-03	2.3E-03
Thyroid	1.7E-04	2.3E-04	4.5E-04	9.2E-04	1.6E-03
Uterus	7.2E-03	8.7E-03	1.2E-02	1.3E-02	2.2E-02
Remaining Organs	2.1E-03	2.6E-03	3.6E-03	4.7E-03	8.0E-03
Effective dose (mSv/MBq)	**1.0E-02**	**1.2E-02**	**1.7E-02**	**2.2E-02**	**3.8E-02**
For an administered activity of 100 MBq (Maximal dose) the effective dose is 1.0 mSv.					

The absorbed dose in the target organ (kidney) is 20 mGy and the typical radiation dose to the critical organ (bladder wall) is 5.6 mGy.					

12 INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

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 93:7 mixture of phosphate solution (1.36 g KH2PO4, adjusted with 0.1 M NaOH to pH 6) and ethanol. Mobile phase B is a 1:9 mixture of water and methanol.

Use an elution program with the following parameters:
Time (min): Flow (ml/min): %A %B
10 1 100 0
15 1 0 100

The technetium(99mTc 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 ³ 95.0% ³ 94.0%
Total front fractions £ 3.0% £ 3.0%
Methanol fraction £ 4.0% £ 4.0%

2 Simplified Sep-Pak rapid procedure.

The 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.
Material:

- Water Sep-Pak C18 Plus short cartridge, 360 mg sorbent per cartridge; product number WAT020515
- Ethanol absolute
- 0.001 M Hydrochloric acid
- Ethanol/Saline (Ethanol - Sodium Chloride solution 9g/L (ratio 1:1))

Stepwise process:

The cartridge (e.g. Sep-Pak C18 Plus short) is washed with 10 ml absolute ethanol, followed by 10 mL 0.001 M hydrochloric acid (HCl). Remaining residues of the solutions are removed by 5 mL of air.

The Technetium (^{99m}Tc) tiatide solution (0.1 mL) is applied on the cartridge. It is important that the column is not dried out during all the different steps. Elute dropwise with 10 mL 0.001 M HCl and collect the eluate. This first eluate contains all hydrophilic impurities.

Next, elute the cartridge dropwise with 10 mL of a solution of ethanol/saline (1:1 v/v). This second eluate contains Technetium (^{99m}Tc) tiatide. The cartridge contains all non-elutable impurities. Use the combined eluted radioactivity plus cartridge as 100%.

Calculation of radiochemical purity:

Activity 2nd eluate * 100%

Combined eluted activity + cartridge

Requirement:

	T = 0	after 8 hours
Technetium (^{99m}Tc) Tiatide	³ 94.0 %	³ 94.0 %
Hydrophilic impurities	£ 3.0 %	£ 3.0 %
Lipophilic impurities	£ 4.0 %	£ 4.0 %

Other information/precautions: The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. Radiation protection precautions in accordance with national regulations must therefore be taken. Waste must be disposed of according to national regulations for radioactive material.