

RENOCIS®

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

RENOCIS®

Kit for the preparation of technetium [^{99m}Tc] succimer injection.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

RENOCIS®, kit for the preparation of technetium [^{99m}Tc] succimer injection, consists of 5 multidose vials, each containing the following sterile, pyrogen-free, freeze-dried product under nitrogen :

Dimercaptosuccinic acid	:	1	mg
Stannous chloride dihydrate	:	0.36	mg
Inositol	:	50	mg
Ascorbic acid	:	0.7	mg

The product contains no antimicrobial preservative.

The product is to be used after reconstitution by the addition of sterile, pyrogen-free, isotonic sodium pertechnetate [^{99m}Tc], allowing the preparation of technetium [^{99m}Tc] succimer injection (technetium [^{99m}Tc] dimercaptosuccinic acid, i.e. technetium [^{99m}Tc] DMSA).

3. PHARMACEUTICAL FORM

Powder for injection.

4. CLINICAL PARTICULARS

4.1. Therapeutic Indications

After reconstitution with sodium pertechnetate [^{99m}Tc] solution the agent may be used for :

Static (planar or tomographic) renal imaging.

- morphological studies of renal cortex.
- individual kidney function.
- location of ectopic kidney.

4.2. Posology and Method of Administration

In adults, the recommended activity is 30 to 120 MBq (0.8-3.2 mCi).

The image acquisitions may be performed as soon as 1 to 3 hours post-injection. Where there is renal impairment or obstruction, delayed views may be needed (6 to 24 hours respectively).

Paediatric dose. The dose for children is adjusted according to body weight :

$$\text{Paediatric dosage (MBq)} = \frac{\text{Adult dosage (MBq)} \times \text{Child weight (kg)}}{70}$$

In some circumstances, dose adjustment according to surface area may be appropriate :

$$\text{Paediatric dosage (MBq)} = \frac{\text{Adult dosage (MBq)} \times \text{Child body surface (m}^2\text{)}}{1.73}$$

4.3. Contra-Indications

None.

4.4. Special Warnings and Special Precautions for Use

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. Interactions with other Medicinal Products and other Forms of Interaction

Some chemical compounds or medicaments may affect the function of tested organs and influence the uptake of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) i.e.,

- ammonium chloride : may substantially reduce renal uptake and increase hepatic uptake of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA),
- sodium bicarbonate : reduction of renal uptake of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA),
- mannitol : reduction of renal uptake of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA).

To avoid these influences, treatment with any of the above chemical products should be interrupted where possible. Care should be taken to ensure the patient is adequately hydrated before scanning.

- Captopril : In patients with unilateral renal artery stenosis, uptake of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) will be impaired in the affected kidney. This is usually reversible after discontinuation of captopril.

4.6. Pregnancy and Lactation

Women of childbearing potential : 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.

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

Lactation : 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 radioactivity in breast milk. If the administration is considered necessary the breast feeding should be interrupted for 12 hours and the expressed feeds discarded. Breast feeding can be restarted when the level in the milk will not result in a radiation dose to the child greater than 1 mSv.

4.7. Effects on Ability to Drive and Use Machines

Effects on ability to drive and use machines have not been described and are not expected.

4.8. Undesirable Effects

Allergic reactions have been reported in the literature although to date these have been inadequately described.

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 or therapeutic 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 effects will occur with low frequency because of the low radiation doses incurred.

For most diagnostic investigations using a nuclear medicine procedure the radiation dose delivered (EDE) is less than 20 mSv. Higher doses may be justified in some clinical circumstances.

4.9. Overdose

In the event of the administration of a radiation overdose with technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) 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

At the chemical concentrations and activities used for diagnostic procedures technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) does not appear to exert any pharmacodynamic effects.

5.2. Pharmacokinetic Properties

After intravenous administration technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) is eliminated from blood with a triphasic pattern in patients with normal renal function. The effective half-life of technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) in blood is around 1 hour. The technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) localizes in high concentrations in renal cortex. Maximal localisation 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 decreased in patients with impaired renal functions.

5.3. Pre-clinical Safety Data

Toxicity with repeated administration of 0.66 mg/kg/day succimer (DMSA) and 0.23 mg/kg/day SnCl₂ over 14 days in rats was not observed. The dose usually administered to humans is 0.14 mg/kg succimer (DMSA). This agent is not intended for regular or continuous administration.

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

5.4. Radiation dosimetry

[^{99m}Tc] technetium decays with the emission of gamma radiation with a mean energy of 140 keV and a half-life of 6 hours, to [^{99m}Tc] technetium which, can be regarded as quasi stable.

For technetium [^{99m}Tc] succimer ([^{99m}Tc] DMSA) the effective dose equivalent resulting from an administered activity of 120 MBq (3.2 mCi) is typically 1.92 mSv (per 70 kg individual).

According to ICRP (International Commission of Radiological Protection) the radiation doses absorbed by the patients are the following :

Organ	ABSORBED DOSE PER UNIT OF ADMINISTERED ACTIVITY (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	1.3E-02	1.6E-02	2.4E-02	3.5E-02	6.0E-02
Bladder wall	1.9E-02	2.4E-02	3.5E-02	5.1E-02	9.4E-02
Bone surfaces	3.5E-03	4.3E-03	6.4E-03	9.9E-03	1.9E-02
Breast	1.8E-03	1.8E-03	2.8E-03	4.5E-03	8.4E-03
Gastrointestinal tract					
Stomach wall	5.5E-03	6.3E-03	9.8E-03	1.3E-02	2.0E-02
Small intestine	5.2E-03	6.4E-03	1.0E-02	1.5E-02	2.5E-02
Upper large intestine wall	5.1E-03	6.3E-03	9.6E-03	1.4E-02	2.3E-02
Lower large intestine wall	3.2E-03	4.2E-03	6.7E-03	1.0E-02	1.8E-02
Kidneys	1.7E-01	2.1E-01	2.9E-01	4.2E-01	7.3E-01
Liver	9.7E-03	1.2E-02	1.8E-02	2.5E-02	4.1E-02
Lungs	2.5E-03	3.5E-03	5.2E-03	8.0E-03	1.4E-02
Ovaries	3.7E-03	4.6E-03	7.2E-03	1.1E-02	2.0E-02
Pancreas	9.0E-03	1.1E-02	1.6E-02	2.3E-02	3.7E-02
Red marrow	6.3E-03	7.5E-03	1.0E-02	1.4E-02	2.0E-02
Spleen	1.3E-02	1.7E-02	2.6E-02	3.8E-02	6.1E-02
Testes	1.8E-03	2.4E-03	3.9E-03	6.2E-03	1.2E-02
Thyroid	1.1E-03	1.9E-03	3.1E-03	5.1E-03	9.2E-03
Uterus	4.6E-03	5.5E-03	8.9E-03	1.3E-02	2.3E-02
Other tissue	3.0E-03	3.6E-03	5.2E-03	8.0E-03	1.4E-02
Effective dose equivalent (mSv/MBq)	1.6E-02	1.9E-02	2.7E-02	4.0E-02	6.9E-02

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Stannous chloride dihydrate
Inositol
Ascorbic acid

6.2. Incompatibilities

None known.

6.3. Shelf-Life

The expiry date for this kit is 12 months from the day of manufacture. The expiry date is indicated on the outer packaging and on each vial.

The expiry date for the labelled product is 8 hours after labelling.

6.4. Special Precautions for Storage

The kit must be stored at a temperature ranging between +2 °C and +8 °C.

The labelled product must be stored at a temperature ranging between +15 °C and +25 °C in accordance with national regulations for radioactive materials.

6.5. Nature and Content of Container

15 mL, colourless, European Pharmacopoeia type I, drawn glass vials, closed with rubber stoppers and aluminium capsules.

6.6. Instructions for Use, Handling and Disposal

- Method of preparation

Usual precautions regarding sterility and radioprotection should be respected.

Take a vial from the kit and put it in an appropriate lead shielding.

Using a hypodermic syringe, introduce through the rubber stopper 1 to 6 mL of sterile pyrogen-free sodium pertechnetate [^{99m}Tc] injection corresponding to maximum 3.7 GBq (100 mCi). Sodium pertechnetate [^{99m}Tc] injection should comply with European Pharmacopoeia specifications. Do not use a breather needle as the contents are under nitrogen : after introduction of the volume of sodium pertechnetate [^{99m}Tc] injection, without removing the needle, withdraw an equivalent volume of nitrogen in order to avoid excess pressure in the vial.

Shake for 5 to 10 minutes.

The obtained preparation is a clear and colourless solution, with a pH ranging between 2.3 and 3.5.

Before use, limpidity of the solution after preparation, pH, radioactivity and gamma spectrum will be checked.

The vial should never be opened and must be kept inside its lead shielding. The solution should be removed aseptically through the stopper with a sterile lead protected syringe.

- Quality control

The quality of labelling (radiochemical purity) could be checked according to the following procedure.

Method

Ascending paper chromatography

Materials and reagents

1. Chromatographic paper
Whatman 1 strip of sufficient length and not less than 2.5 cm wide.
Trace two fine lines parallel to the ends of the strips, the one being called "deposit line" at 2.5 cm, the other one being called "solvent line" at 10 cm from the "deposit line".
2. Mobile phase
methyl ethyl ketone
3. Glass tank
Glass tank of suitable size for the chromatographic paper used, ground at the top to take a closely fitting lid. In the top of the tank is a device which suspends the chromatographic paper and is capable of being lowered without opening the chamber.
4. Miscellaneous
Forceps, scissors, syringes, needles, appropriate counting assembly.

Procedure

1. Place into the glass tank a layer 2 cm deep of the mobile phase.
2. Apply a spot of the preparation to the "deposit line" of the paper strip using a syringe and needle and dry in air.
3. Using forceps, insert the paper strip into the tank and close the lid. Lower the paper into the mobile phase and allow the solvent to migrate to the "solvent line".
4. Remove the paper strip with forceps and dry in air.
5. Determine distribution of radioactivity with an appropriate detector.
Identify each radioactive spot by calculating the Rf. The Rf of technetium [^{99m}Tc] succimer is 0, and that of pertechnetate ion (free [^{99m}Tc] technetium) is 1.
Measure the radioactivity of each spot by integration of the peaks.

6. Calculations
Calculate the percentage of technetium [^{99m}Tc] succimer (radiochemical purity)

$$\% \text{ technetium } [^{99m}\text{Tc}] \text{ succimer} = \frac{\text{Radioactivity of the spot at Rf 0}}{\text{Total radioactivity of the paper strip}} \times 100$$

Calculate the percentage of free [^{99m}Tc] technetium

$$\% \text{ free } [^{99m}\text{Tc}] \text{ technetium} = \frac{\text{Radioactivity of the spot at Rf 1}}{\text{Total radioactivity of the paper strip}} \times 100$$

7. The percentage of technetium [^{99m}Tc] succimer (radiochemical purity) should be at least 95 % and the percentage of free [^{99m}Tc] technetium should not be greater than 2 %.

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. Radioactive waste must be disposed of in conformity with the relevant national and international regulations.

ADMINISTRATIVE DATA

7. MARKETING AUTHORISATION HOLDER

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91192 Gif-sur-Yvette Cedex
FRANCE
Tel. : +33-(0)1.69.85.70.70
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8. MARKETING AUTHORISATION NUMBER

PL 11876/0008

9. RENEWAL OF AUTHORISATION

16 July 2003

10. DATE OF REVISION OF THE TEXT

05/2006