TECHNICAL LEAFLET

RENON

Multidose kit

Kit for use in the preparation of Technetium-99m Diethylene triamine pentaacetate (DTPA) Injection

Code No.: MR-11
Hungarian Licence No.: OGYI-T-8816/01
ATC code: V09C A 01

QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active ingredient:

Acidum diaethylentriamino-pentaaceticum	10.0 mg

Other ingredients:

Stannous(II) Chloride Dihydrate	0.50 mg
Natrium aceticum trihydratum	40.0 mg
Acidum ascorbicum	0.10 mg

The product is to be used after reconstitution of the kit labelling with addition of sterile sodium pertechnetate (^{99m}Tc) solution for injection.

PHARMACEUTICAL FORM

The kit containing 6 vials of lyophilised, sterile, pyrogen free and inactive preparation sealed in nitrogen atmosphere, ready for one-step labelling with Sodium Pertechnetate [^{99m}Tc] Injection Ph.Eur. to yield a diagnostic radiopharmaceutical imaging agent. Labels for the reconstituted product and sanitising swabs (containing 70% isopropyl alcohol) are provided.

CLINICAL PARTICULARS

Diagnostic indications

After labelling with sodium pertechnetate (^{99m}Tc) solution the compound may be used for:

a. After reconstitution with sodium pertechnetate(Tc-99m) solution the agent may be used for:
   - Dynamic renal scintigraphy for perfusion, function and urinary tract studies.
   - Measurement of glomerular filtration rate.
   - Cerebral angiography and brain scanning. As an alternative method, when computed tomography and/or magnetic resonance imaging are not available.

b. After inhalation of the nebulized technetium(Tc-99m) labelled substance :
   - Lung ventilation imaging.

c. After oral administration of the technetium(Tc-99m) labelled substance :
   - Studies of gastro-oesophageal reflux and gastric emptying.

Posology and method of administration

In adults, the following administered doses are recommended (other doses may be justifiable).

For intravenous use :

- Measurement of glomerular filtration rate from plasma: 1.8-3.7 MBq.
- Measurement of glomerular filtration rate using gamma camera combined with sequential dynamic renal scanning: 37-370 MBq. Sequential scanning should begin immediately after injection. Optimal static imaging time is 1-hour post injection.
- Brain scanning: 185-740 MBq.

For cerebral examinations, static images are obtained 1 hour and, if necessary, several hours after injection. Sequential dynamic scanning should begin immediately after injection.

For inhalation:

- Lung ventilation imaging:
  500-1000 MBq in nebuliser
  50-100 MBq in lung.

For oral use :

Study of gastro-oesophageal reflux and gastric emptying: 10-20 MBq.
Dynamic recording should be performed during the first minutes (up to 120 minutes for gastroduodenal transit).

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

$$\text{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child weight (kg)}}{70\ \text{kg}}$$

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

$$\text{Paediatric dose (MBq)} = \frac{\text{Adult dose (MBq) x child body surface (m}^2\text{)}}{1.73\ (\text{m}^2)}$$

In very young children (up to 1 year) a minimum dose of 20 MBq is necessary in order to obtain images of sufficient quality, when technetium(Tc-99m) pentetate (DTPA) is used for kidney studies.

Contra-indications

None

Special warnings and special precautions for use

Special 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.

Special precautions for use

In case of reduced renal function the radiation exposure can be increased, this should be considered in the assessment of the activity to be administered. To reduce the radiation dose to the bladder, good hydration and frequent voiding of urine is recommended.

Interaction with other medicaments and other forms of interaction

Many drugs may affect the function of tested organ and modify the uptake of technetium(Tc-99m) pentetate (DTPA) i.e.,

Diagnostic use of captopril: Dynamic renal scanning performed under control conditions and again one hour after oral administration of captopril (25-50 mg) may reveal haemodynamic changes in a kidney affected by renal artery stenosis. The blood pressure should be carefully monitored as patients with vascular disease are at risk of significant hypotension and renal impairment.

Diagnostic use of frusemide: The administration of intravenous frusemide during dynamic renal scanning increase elimination of technetium(Tc-99m) pentetate (DTPA) which may help to distinguish whether true obstruction exists in a dilated renal tract.

Cerebral angiography: Phychotropic drugs increase blood flow in the territory of the external carotid artery. This may lead to the rapid uptake of tracer in the nasopharyngeal area during the arterial and capillary phases (hot nose phenomenon).

Pregnancy and lactation

Women of childbearing potential

When it is necessary to inject radiopharmaceuticals to women of childbearing potential, information should always be thought about pregnancy. Any woman who has missed a period should be assumed to be pregnant until proven otherwise. Where uncertainly 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 always considered.

Pregnancy

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

Lactation

Before administering radiopharmaceuticals to a mother who is breast feeding consideration should be given as to whether the investigation could be reasonably delayed until after the mother has ceased breast feeding and as to whether the most appropriate choice of radiopharmaceuticals 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 12 hours and the expressed feeds discarded.

Effects on ability to drive and use machines

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

Undesirable effects

There are no side effects or adverse reactions and no specific contra-indications. 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. The effective dose equivalent delivered from radiation dose of most diagnostic investigation is less than 20 mSv.

Overdose

In the event of the administration of a radiation overdose with technetium(Tc-99m) pentetate (DTPA) 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.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

ATC code: V09C A01

At the chemical concentrations and activities used for diagnostic procedures technetium(Tc-99m) pentetate (DTPA) does not appear to exert any pharmacodynamic effects.

Pharmacokinetic properties

Following intravenous injection, technetium(Tc-99m) pentetate (DTPA) rapidly distributes throughout the extracellular fluid. Less than 5 % of the injected dose is bound to the plasma proteins. There is also a negligible binding of technetium(Tc-99m) pentetate (DTPA) to red blood cells. Technetium(Tc-99m) pentetate (DTPA) does not cross the normal blood-brain barrier but diffuse weakly in breast milk. Plasma clearance is multiexponential with an extremely fast component. The complex remains stable in vivo, more than 98 % of urine radioactivity is in the form of a chelate. Approximately 90 % of the injected dose is eliminated in the urine within the first 24 hours mainly by glomerular filtration. No retention of the compound has been demonstrated in the kidneys. Plasma clearance may be delayed in patients with renal disease.

In subjects exhibiting oedema or ascites, distribution of the radionuclide in the extracellular space may be modified.

In lung ventilation studies, after inhalation, technetium(Tc-99m) pentetate (DTPA) diffuses rapidly from the pulmonary alveoles towards the vascular space where it is diluted. The half life of technetium(Tc-99m) pentetate (DTPA) in the lungs is slightly less than 1 hour. Many factors are likely to modify the permeability of the pulmonary epithelium like cigarette smoking.

Following oral administration, technetium(Tc-99m) pentetate (DTPA) does not pass through the digestive barrier.

Preclinical safety data

This agent is not intended for regular or continuous administration.Repeated intravenous administration of $CaNa_3DTPA$ to rabbits and dogs for 14 days of doses that were 100 and 1000 times (respectively) the normal dose for human, produced no evidence of toxicity.The minimum dose of CaDTPA causing abortion and foetal death in mice was approximately 3600 times the dose of $CaNa_3DTPA$ that is proposed for diagnosis in women. Mutagenicity studies and long-term carcinogenicity studies have not been carried out.

Radiation dosimetry

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

For this product the effective dose equivalent resulting from :

- an intravenous administered activity of 740 MBq to a patient with normal renal function is 4.7 mSv (per 70 kg individual).
- an inhalation (nebuliser) of 100 MBq is 0.7 - 7 mSv (per 70 kg individual).
- an oral administration of 20 MBq is 0.5 mSv (per 70 kg individual).

According to ICRP 53 (International Commission of Radiological Protection) the radiation doses absorbed by the patients are the following:

Normal renal function

^{99m}Tc-RENON ORGAN	Absorbed dose per unit activity administered by intravenously (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	1.4E-03	1.8E-03	2.7E-03	4.2E-03	7.8E-03
Bladder walls	6.5E-02	8.1E-02	1.2E-01	1.7E-01	3.2E-01
Bone surfaces	1.7E-03	2.1E-03	3.1E-03	4.6E-03	8.5E-03
Breast	9.4E-04	9.4E-04	1.4E-03	2.2E-03	4.3E-03
Stomach wall	1.3E-03	1.7E-03	2.8E-03	4.1E-03	7.5E-03
Small intestine	2.6E-03	3.1E-03	5.0E-03	7.5E-03	1.3E-02
ULI wall	2.2E-03	2.9E-03	4.4E-03	7.1E-03	1.2E-02
LLI wall	4.2E-03	5.4E-03	8.2E-03	1.1E-02	1.9E-02
Kidneys	4.4E-03	5.4E-03	7.7E-03	1.1E-02	2.0E-02
Liver	1.3E-03	1.6E-03	2.5E-03	3.9E-03	7.0E-03
Lungs	1.0E-03	1.3E-03	2.0E-03	3.1E-03	5.7E-03
Ovaries	4.3E-03	5.3E-03	7.8E-03	1.1E-02	1.8E-02
Pancreas	1.5E-03	1.8E-03	2.9E-03	4.5E-03	8.1E-03
Red Marrow	2.5E-03	3.0E-03	4.2E-03	5.7E-03	8.7E-03
Spleen	1.4E-03	1.7E-03	2.5E-03	4.0E-03	7.2E-03
Testes	2.8E-03	4.1E-03	6.8E-03	1.0E-02	1.9E-02
Thyroid	7.9E-04	1.3E-03	2.1E-03	3.4E-03	6.1E-03
Uterus	7.9E-03	9.6E-03	1.5E-02	2.1E-02	3.5E-02
Other tissue	1.7E-03	2.0E-03	3.1E-03	4.6E-03	8.3E-03
Effective dose equivalent (mSv/MBq)	6.3E-03	7.8E-03	1.1E-02	1.7E-02	3.0E-02

Abnormal renal function

^{99m}Tc-RENON ORGAN	Absorbed dose per unit activity administered by intravenously (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	4.1E-03	5.1E-03	7.8E-03	1.2E-02	2.1E-02
Bladder walls	2.2E-02	2.7E-02	4.0E-02	5.8E-02	1.1E-01
Bone surfaces	4.4E-03	5.3E-03	7.9E-03	1.2E-02	2.1E-02
Breast	3.0E-03	3.0E-03	4.3E-03	6.9E-03	1.3E-02
Stomach wall	3.8E-03	5.0E-03	7.9E-03	1.1E-02	2.0E-02
Small intestine	4.7E-03	5.6E-03	8.6E-03	1.3E-02	2.3E-02
ULI wall	4.4E-03	5.6E-03	8.1E-03	1.3E-02	2.2E-02
LLI wall	4.7E-03	6.2E-03	9.6E-03	1.4E-02	2.5E-02
Kidneys	7.9E-03	9.6E-03	1.4E-02	2.0E-02	3.4E-02
Liver	3.8E-03	4.6E-03	7.1E-03	1.1E-02	1.9E-02
Lungs	3.3E-03	4.2E-03	6.2E-03	9.5E-03	1.7E-02
Ovaries	4.9E-03	6.3E-03	9.4E-03	1.4E-02	2.4E-02
Pancreas	4.3E-03	5.4E-03	8.1E-03	1.2E-02	2.2E-02
Red Marrow	5.2E-03	6.3E-03	9.0E-03	1.3E-02	2.2E-02
Spleen	4.0E-03	4.8E-03	7.2E-03	1.1E-02	2.0E-02
Testes	3.3E-03	4.5E-03	6.9E-03	1.1E-02	2.0E-02
Thyroid	2.5E-03	4.3E-03	6.8E-03	1.1E-02	1.9E-02
Uterus	6.3E-03	7.5E-03	1.1E-02	1.7E-02	2.9E-02
Other tissue	3.3E-03	4.0E-03	6.1E-03	9.4E-03	1.7E-02
Effective dose equivalent (mSv/MBq)	**5.3E-03**	**6.6E-03**	**9.7E-03**	**1.5E-02**	**2.6E-02**

The radiation doses given to man on administration by aerosol of ^{99m}Tc-RENON are the following

^{99m}Tc-RENON ORGAN	Absorbed dose per unit activity administered (mGy/MBq)				
	Adult	15 years	10 years	5 years	1 year
Adrenals	2.1E-03	2.9E-03	4.4E-03	6.7E-03	1.2E-02
Bladder walls	4.7E-02	5.8E-02	8.4E-02	1.2E-01	2.3E-01
Bone surfaces	1.9E-03	2.4E-03	3.5E-03	5.3E-03	9.8E-03
Breast	1.9E-03	1.9E-03	3.3E-03	4.8E-03	7.8E-03
Stomach wall	1.7E-03	2.2E-03	3.5E-03	5.1E-03	8.9E-03
Small intestine	2.1E-03	2.6E-03	4.1E-03	6.3E-03	1.1E-02
ULI wall	1.9E-03	2.4E-03	3.8E-03	6.1E-03	1.0E-02
LLI wall	3.2E-03	4.2E-03	6.3E-03	8.8E-03	1.5E-02
Kidneys	4.1E-03	5.1E-03	7.2E-03	1.1E-02	1.9E-02
Liver	1.9E-03	2.5E-03	3.7E-03	5.5E-03	9.7E-03
Lungs	1.7E-02	2.6E-02	3.6E-02	5.4E-02	1.0E-01
Ovaries	3.3E-03	4.1E-03	6.1E-03	8.9E-03	1.5E-02
Pancreas	2.1E-03	2.6E-03	4.0E-03	6.1E-03	1.1E-02
Red Marrow	2.7E-03	3.4E-03	4.7E-03	6.2E-03	9.6E-03
Spleen	1.9E-03	2.4E-03	3.6E-03	5.6E-03	9.9E-03
Testes	2.1E-03	3.1E-03	5.2E-03	7.9E-03	1.5E-02
Thyroid	9.9E-04	1.7E-03	2.7E-03	4.4E-03	7.8E-03
Uterus	5.9E-03	7.2E-03	1.1E-02	1.6E-02	2.7E-02
Other tissue	1.8E-03	2.2E-03	3.2E-03	4.9E-03	8.6E-03
Effective dose equivalent (mSv/MBq)	**7.0E-03**	**9.1E-03**	**1.3E-02**	**2.0E-02**	**3.6E-02**

The radiation doses given to man on administration per os of ^{99m}Tc-RENON are the following

Organ	Absorbed dose per unit activity administered (mGy/MBq)
Stomach	8.6E-02
Small intestine	7.0E-02
Red marrow	1.2E-03
Ovaries	3.5E-03
Testes	1.7E-03
Effective dose equivalent (mSv/MBq)	**2.5E-02**

PHARMACEUTICAL PARTICULARS

List of excipients

Stannous(II) Chloride Dihydrate
Sodium aceticum trihydratum
Acidum ascorbicum

Incompatibilities

None known.

Shelf life

Shelf life of RENON in vivo kit (lyophilised non-radioactive components in glass ampoules closed with a rubber stopper and plastic-aluminium caps with turned up edge) is 24 months from the day of production. One paper box contains 6 ampoules. Radioactive labelling of the content of the individual ampoules can be done at different occasions within the expiry date shown on the label of the ampoule and the paper box. ^{99m}Tc-RENON injections must be used within 6 hours from labelling. The labelling procedure should be carried out in closed system.

Special precaution for storage

RENON in vivo kit is to be stored at temperature below 25°C in its original packaging protected from light. ^{99m}Tc-DTPA injection is to be stored at temperature below 25°C in accordance with the national regulations on radioactive materials. This product is not to be administered directly to the patient. The contents of the vial are intended only for use in the preparation of radioactive ^{99m}Tc-technetium labelled injection, using the procedure described in user package insert. Radiopharmaceutical should be used only by physicians who are qualified by training and experience in the safe use and handling of radionuclides and whose experience and training have been approved by the appropriate government agency authorized to licence the use of radionuclides.

Nature and contents of container

Sterile, 8 ml, colourless, European Pharmacopoeia type I, glass vials, closed with sterile rubber stopper and plastic-aluminium caps with turned up edge. Six vials are enclosed in a cardboard box.

Instruction for use, handling and disposal

Method of preparation

It is recommended that the contents of the vials should be reconstituted using sterile sodium pertechnetate(Tc-99m) free from any oxidising agent and to use as a diluter a 0.9% sterile solution of sodium chloride for additive-free injection. Preparation and use of the diagnostic agent should be carried out under aseptic conditions.

Determine the activity necessary according to the dose to be administered, the number of patients and the decay of the technetium-99m. The total activity per vial should not exceed 8.0 GBq. The final volume of the preparation should be between 1 and 5 ml. Place a vial of RENON in a lead container. Disinfect the vial septum using a bacteriostatic agent.

Inject aseptically into the vial the appropriate volume of sodium pertechnetate(Tc-99m) and the required quantity of diluter so as to be within the volume and activity limits of the preparation. Withdraw a volume of gas, equivalent to the volumes of the solutions, in order to balance the pressures. Invert the vial several times in order to homogenise the preparation. Leave to react for a minimum of 15 minutes before use. Measure the activity using a correctly calibrated monitor. Complete the label using the marking parameters and label the vial and lead container. Ascending chromatography can check the labelling yield.

Keep the preparation under suitable shielding at room temperature and away from light.

Determination of the Labelling Yield

Ascending chromatography can check the labelling yield. The chromatography conditions are set out in the table below.

	Colloidal ^{99m}Tc	**$^{99m}TcO_4^-$**
Chromatography conditions		
Plate	ITLC-SG (Gelman)	ITLC-SG (Gelman)
Mobile phase	0.9% NaCl	Methyl ethyl ketone
Development length	10 - 15 cm	10 - 15 cm
Development time	10 minutes	10 minutes
Characteristics R_f	Colloidal form: 0.0 - 0.1 Complex + $^{99m}TcO_4^-$: 0.9 - 1.0	Complex + colloid: 0.0-0.1 free $^{99m}TcO_4^-$: 0.9 - 1.0

The sum of the activities due to the colloidal form and the free pertechnetate(Tc-99m) form, corresponding to the impurities in the two chromatograms, must not exceed 5 % of the total activity.

Additional requirements

The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. National regulations for radioactive materials must be applied in the radiation protection precautions and waste disposal.

MARKETING AUTHORISATION HOLDER

MEDI-RADIOPHARMA Ltd
2030 Érd, Szamos u.10-12.
HUNGARY

MARKETING AUTHORISATION NUMBER

Hungary: OGYI-T-8816/01

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