

## TECHNICAL LEAFLET

### MERCAPTON

Multidose kit  
Kit for use in the preparation of Technetium-99m Dimercapto succinic acid (DMSA) Injection

Code No.: MR-13  
Hungarian Licence No.: OGYI-T-9940/01  
ATC code: V09A A 02

### QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains:

Active ingredient:

Meso-2-3- dimercapto succinic acid 3.00 mg

Other ingredients:

Stannous(II) Chloride Dihydrate 0.33 mg

Sodium aceticum trihydratum 32.8 mg

Acidum ascorbicum Ph.Eur. 0.10 mg

The product is to be used after reconstitution of the kit labelling with addition of sterile sodium pertechnetate (<sup>99m</sup>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 [<sup>99m</sup>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 reconstitution with sodium pertechnetate [<sup>99m</sup>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

#### Posology and method of administration

In adults, (average weight of 70kg) the recommended activity is 50 to 140 MBq.

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

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:

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

#### Contra-indications

None

### 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.

### Interaction with other medicaments and other forms of interaction

Some chemical compounds or medicaments may affect the function of tested organs and influence the uptake of technetium [<sup>99m</sup>Tc] succimer (DMSA) i.e.

ammonium chloride: may substantially reduce renal uptake and increase hepatic uptake of technetium [<sup>99m</sup>Tc] succimer (DMSA).

sodium bicarbonate: reduction of renal uptake of technetium [<sup>99m</sup>Tc] succimer (DMSA).

mannitol: reduction of renal uptake of technetium [<sup>99m</sup>Tc] succimer (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 [<sup>99m</sup>Tc] succimer (DMSA) will be impaired in the affected kidney. This is usually reversible after discontinuation of captopril.

### 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 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 always be 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

The product has no direct influence on ability of car driving.

### Undesirable effects

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 [<sup>99m</sup>Tc] succimer (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.

### PHARMACOLOGICAL PROPERTIES

#### Pharmacodynamic properties

ATC code: V09A A02

At the chemical concentrations and activities used for diagnostic procedures technetium [<sup>99m</sup>Tc] (DMSA) does not appear to exert any pharmacodynamic effects.

The structure of DMSA-complex administered to the body is [<sup>99m</sup>Tc-(DMSA)<sub>2</sub>], i.e. it is a biscomplex. Its 75% binds to the plasma proteins of the blood. Binding highly depends upon which pH value was ensured by the buffer of the kit. Optimum pH is in the range of 3-4.

[<sup>99m</sup>Tc-(DMSA)<sub>2</sub>] is taken up by the kidneys in form bound to the plasma proteins. One of the ligands is replaced by an -SH group of the receptor in the tubules (especially in the proximal ones), a [<sup>99m</sup>Tc-(DMSA)-receptor] complex is formed, one DMSA molecule gets free and is excreted with the urine. This mechanism results in binding of 0.1 mg DMSA per kg body.

Since the proximal tubules are situated in the cortex of the kidneys, imaging is formed by visualising the cortex itself. 40-50% of the injected activity appears in the kidney cortex and approximately 3% in the liver. In case of patient with impaired kidney function this ratio decreases and the radioactivity of the liver increases significantly.

Finally, <sup>99m</sup>Tc-(DMSA) bound in the kidneys is excreted with the urine.

#### Pharmacokinetic properties

After intravenous administration technetium [<sup>99m</sup>Tc] succimer (DMSA) is eliminated from blood with a triphasic pattern in patients with normal renal function. The effective half-life of technetium [<sup>99m</sup>Tc] succimer (DMSA) in blood is around 1 hour. The technetium [<sup>99m</sup>Tc] succimer (DMSA) localises 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 localise in the liver. However, this amount can be increased significantly and renal distribution decreased in patients with impaired renal functions.

#### Preclinical safety data

meso-2,3-Dimercaptosuccinic acid is a known metal chelate and has been administered intravenously in gram quantities to human subjects in the treatment of heavy metal poisoning. Given intraperitoneally, its LD<sub>50</sub> in mice is reported to be 3.163 g/kg; given subcutaneously, its LD<sub>50</sub> in mice was reported to be 1.725 g/kg in one study and 2.73 g/kg in another. Pursuant to intravenous acute toxicity experiments on mice no clinical symptoms can be observed up to 0.43 mg/kg body. If administered as prescribed minimum 0.115 mg, maximum 3.0 mg of <sup>99m</sup>Tc-DMSA is introduced to the body. Pursuant to intravenous acute toxicity experiments on mice no clinical symptoms can be observed up to 0.43 mg/kg body. In case as the result of an error or a mistake of the personnel the whole content of one vial is injected, it represents 3.0 mg, which equals to 0.04285 mg/kg body (for 70 kg average body weight). This only 9-97 % of the symptom-free limit. Consequently, the application of the medical product is to be considered as safe. Further advantage of the medical product is that the activity of the applied Tc-99m-pertechnetate (max. of 3.7 GBq) has no effect on the quantity of the radiochemical impurities, i.e. their total quantity remains below 10% permitted. Therefore, application of the medical product can be considered safe from the point of view of labelling.

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

#### Radiation dosimetry

[<sup>99m</sup>Tc] technetium decays with the emission of gamma radiation with a mean energy of 140keV and a half-life of 6 hours, to [<sup>99</sup>Tc] technetium which, can be regarded as quasi-stable. For technetium [<sup>99m</sup>Tc] succimer (DMSA) the effective dose equivalent resulting from an administered activity of 140 MBq is typically 2.24 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 activity administered (mGy/MBq) |                |                |                |                |
|--|--|----------------|----------------|----------------|----------------|
|  | Adult  | 15 year        | 10 year        | 5 year         | 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        |
| 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        |
| ULI wall                                   | 5.1E-03  | 6.3E-03        | 9.6E-03        | 1.4E-02        | 2.3E-02        |
| LLI 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        |
| <b>Effective dose equivalent (mSv/MBq)</b> | <b>1.6E-02</b>   | <b>1.9E-02</b> | <b>2.7E-02</b> | <b>4.0E-02</b> | <b>6.9E-02</b> |

## PHARMACEUTICAL PARTICULARS

### List of excipients

Stannous(II) Chloride Dihydrate  
Natrium aceticum trihydratum  
Acidum ascorbicum

### Incompatibilities

Tin (II) chloride of reducing capability is present in the ampoules of MERCAPTAN in vivo kit. (It reduces free pertechnetate (+7) into technetium of +4 oxidation degree, which readily forms a complex entity with DMSA ligand.) Therefore, the content of the ampoules is incompatible with oxidising media (oxidising agents, oxygen of the air, etc.) and moisture. Alkaline media also supports the oxidation of tin (II) before conducting the labelling process. Therefore, incompatibility exists with any chemical bases. Consequently, the cap and the plug of the ampoules can only be removed right before the radioactive labelling, which should be carried out strictly according to the instructions for handling any use of the product. No interaction with other pharmaceuticals has been reported.

### Shelf life

Shelf life of MERCAPTAN in vivo kit (lyophilised non-radioactive components in glass ampoules closed with a rubber stopper and plastic-aluminium caps with turned up edge) is 12 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. <sup>99m</sup>Tc-MERCAPTAN (DMSA labelled with radioactive Tc-99m radionuclide) injection must be used within 6 hours from labelling. The labelling procedure should be carried out in closed system.

### Special precaution for storage

MERCAPTAN in vivo kit is to be stored below 25°C in its original packaging.

<sup>99m</sup>Tc-DMSA 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 <sup>99m</sup>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.

### Instruction for use, handling and disposal

Usual precaution regarding sterility and radioprotection should be respected.

The administration of radiopharmaceutical 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.

### Method of preparation of the final dosage form for injection

Use aseptic technique throughout.

- Place one of the vials in a suitable shielding container and swab the rubber closure with the sanitising swab provided.
- Using a suitable syringe, inject a suitable quantity (see notes 1 and 2) of the eluate from a technetium-99m sterile generator into the shielded vial. Before removing the syringe from the vial, withdraw an equivalent volume of gas from the space above the solution to normalise the pressure in the vial.
- Invert the vial several times to ensure complete dissolution of the powder. Leave to react for a minimum of 15 minutes before use.
- Assay the total activity, complete the label provided and attach to the vial. The radiochemical purity can be determined as given below.

### Notes:

- Up to 3.7 GBq (100mCi) technetium-99m may be added to the vial.
- Reconstitute with 2-5ml.
- The use of a technetium-99m pertechnetate solution complying with the specification prescribed by the USP and BP/Ph. Eur. on Sodium Pertechnetate [<sup>99m</sup>Tc] Injection will yield a preparation of an appropriate quality.

### Radiochemical purity measurement

Examine by thin-layer chromatography using silica gel as the coating substance on a glass-fibre sheet. Heat the plate at 110 °C for 10 min. Use a plate such that during development the mobile phase migrates over a distance of 10 cm to 15 cm in about 10 min. Apply to the plate 5 µl of the injection to be examined. Develop immediately over a path of 10 cm to 15 cm using methyl ethyl ketone R. Allow the plate to dry. Determine the distribution of radioactivity using a suitable detector. Technetium succimer complex remains at the starting point. Pertechnetate ion migrates near to the solvent front. Not less than 95.0 per cent of the total radioactivity is found in the spot corresponding to technetium succimer complex. The radioactivity corresponding to pertechnetate ion represents not more than 5.0 per cent of the total radioactivity. The administration of radiopharmaceuticals creates risks for other persons from external radiation or contamination from spills of urine, vomiting, etc. National regulations for radioactive material must be applied in the radiation protection precautions and waste disposal.

### MARKETING AUTHORISATION HOLDER

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HUNGARY

### MARKETING AUTHORISATION NUMBER

Hungary: OGYI-T-9940/01

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