# SUMMARY OF PRODUCT CHARACTERISTICS

## 1. NAME OF THE MEDICINAL PRODUCT

MON.DTPA KIT 35 mg lyophilized powder for I.V. injection in a vial

## 2. QUALITATIVE AND QUANTITATIVE COMPOSITION

**Active Ingredient**
Diethylene triamine penta acetic acid calcium trisodium hydrate 35 mg

**Excipients**
Sodium hydroxide ……qs (for pH adjustment)
Sodium chloride (0.9 % NaCl) …… qs

See section 6.1 for a full list of excipients

There is no radioisotope substance in the formulation of MON.DTPA KIT before labelling with Technetium-99m (Tc-99m) sodium pertechnetate.

## 3. PHARMACEUTICAL FORM

Sterile, non-pyrogenic lyophilized powder
White powder in glass vial.

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

MON.DTPA KIT is only for diagnostic use.
After being labelled with Tc-99m Pertechnetate, obtained Tc-99m-DTPA is used for the following indications.

Renal:
- In the diagnosis of urinary system diseases by the dynamic kidney scintigraphy,
- In the calculations of glomerular filtration rate (GFR),
- In the evaluation of kidney perfusion and relative kidney functions,

Neurology:
- In the imaging of pathologies disrupting blood-brain barrier,
- In the identification of brain death,
- In the evaluation of cerebrospinal fluid (CSF) dynamic by the cisternoscintigraphy, (See warnings and precautions section for intrathecal use.)

Pulmonary:
- In the diagnosis of lung diseases by the lung ventilation scintigraphy (by using nebulizer),

Gastroenterology:
- In the diagnosis of gastroesophageal reflux,
- In the measurement of stomach discharge time,
- In the measurement of esophageal passage time.

## 4.2 Posology and method of administration

**Posology**
The administration doses recommended for adults (70 kg) are specified below.
- For the kidney scintigraphy and the measurement of glomerular filtration rate: 111-185 MBq (3-5 mCi)
- For the brain scintigraphy: 185-740 MBq (5-20 mCi)
- For the analysis of CSF dynamic by cisternoscintigraphy: 37-111 MBq (1-3 mCi) is applied intrathecally. (See warnings and precautions)
- For the lung ventilation scintigraphy: 500-1000 MBq is put into the nebulizer. It is inhaled so that the dose to reach to the lungs is 50-100 MBq.
- For the analyses of gastroesophageal reflux and stomach discharge time: 10-20 MBq is applied orally with liquid, solid or semi-solid foods.

**Administration frequency and time**
In the literature, it is stated that the complete formation of target/non-target rate in intracranial lesions can be completed within few hours. The possibility of failing in the imaging of some lesions in the images taken early should be kept in mind.

**Method of administration**
MON.DTPA KIT is a sterile, non-pyrogenic lyophilized powder. It is administered to the patient by intravenous, intrathecally, by inhalation and orally according to its intended use after in vitro radio labelling with Tc-99m.

**Additional information on special populations**

**Renal/hepatic impairment**

The image quality may be adversely affected in the patients with weak or impaired kidney function.

**Paediatric population**
Administration to children, the following Webster formula is applied. See the section 4.3 in order to adjust the activity and decide.

$$Ac = \frac{[(N+1)xAy]}{N+7}$$

N = age of the child (year)
$A_{ç}$, $A_y$ = radioactivity determined for children and adults [MBq]

**Geriatric population**
There is no special use.

## 4.3 Contraindications
It is contraindicated in the patients who have hypersensitivity against radiopharmaceutical products or any of the substances contained in the compound of the product.

## 4.4 Special warnings and precautions for use

RADIOPHARMACEUTICALS SHOULD BE ADMINISTERED ONLY BY NUCLEAR MEDICINE PHYSICIANS IN NUCLEAR MEDICINE CENTERS.

The content of the kit is sterile and non-pyrogenic. The preparation process should be carried out definitely under aseptic conditions.

The content of the kit is not radioactive before adding Tc-99m-sodium pertechnetate solution. The solution prepared by adding Tc-99m- is radioactive and should be necessarily kept in lead shielded container.

The sodium pertechnetate solution containing oxidant agent may cause adverse effect in the processes of preparing radiopharmaceuticals. For this reason, the content of the sodium pertechnetate solution used is important.

The content of the kit vial is used for preparing Tc-99m-DTPA by combining with Tc-99m solution. The content of the kit, not labelled with Tc-99m solution, CANNOT BE INJECTED directly to the patient. For reducing the radiation dose of the bladder, the patient should be warned to drink plenty of liquid and to urinate up to 4-6 hours after the completion of the administration.

Tc-99m-DTPA solution should be stored below 25 $^{0}$C at room temperature and should be disposed after 8 hours. If the prepared solution is cloudy, it should not be used.

This medicinal product contains sodium less than 1 mmol (23 mg) in each ml. Therefore, any caution related to sodium is not required.

It does not contain preservative substance. Therefore, it can be administered intrathecally in order to evaluate CSF dynamic. Administration by this method, the maximum amount of active substance to be administered to the patient should not exceed 1 mg, the bacterial endotoxin limit should not be more than 14 EU in the volume containing the patient dose.

## 4.5 Interactions with other medicinal products and other forms of interaction

In application:

- Medications containing aluminum cause to receive abnormal glomerular filtration results,
- Diuretic medications cause to misdiagnose by reinforcing the renal function.

**Additional information on special populations**

No study was carried out on interaction concerning special population.

**Paediatric population**

No study was carried out on interaction peculiar to children.

**Geriatric population**

No additional information about geriatric population is available.

## 4.6 Pregnancy and lactation

**General recommendation**
Pregnancy category: C

**Women of childbearing potential / Contraception**
The effects of Tc-99m-DTPA on fertility are not known.

**Pregnancy**
Adequate data regarding the use of Tc-99m-DTPA in pregnant women is not available.

The studies on animals are insufficient in terms of the effects on pregnancy / and-or / embryonic / fetal development / and-or / birth / and-or / post-partum development. (See section 5.3). The potential risk to people is unknown.
MON.DTPA KIT should not be used in pregnancy period unless it is necessary (Tc-99m-DTPA application, in the cases where the expected benefit is higher than the potential damage).
In such a case, the physician should act very carefully and apply the lowest activity dose possible.

**Lactation**
Tc-99m pertechnetate is excreted in breast milk. For this reason, breast milk should not be given to babies fed with breast milk during at least 12 hours after Tc-99m-DTPA administration to mother.

**Fertility**
The long term animal experiments concerning that Tc-99m-DTPA influences the fertility and/or may have carcinogenic effect in men and women are not available in literature.

The effect of Tc-99m-DTPA on fertility is unknown. The ideal time for administration to women at the age of fertility is 10 days following the end of menstruation.

## 4.7 Effects on ability to drive and use machines
Tc-99m-DTPA administration has no adverse effect on driving and using machines.

## 4.8 Undesirable effects
Undesirable effects are listed according to the following level of frequency:
Very common (≥1/10); common (≥1/100 or <1/10 ); uncommon ( ≥1/1000 or < 1/100); rare (≥1/10.000 or < 1/1000 ); very rare (<1/10.000 ); unknown.

It is stated in the literatures that vasomotor problems related to Tc-99m-DTPA usage may occur, but there is no information about its frequency. The side effects reported in the literatures are given below.

**Vascular diseases**
Hypotension

**Skin and subcutaneous tissue diseases**
Reddening on face
Itching
Urticaria

There are reported more serious problems arising from misformulations and misadministrations in the application of DTPA aerosol and intrathecal (into cerebrospinal fluid) injection.

Exposure to ionized radiation may initiate the formation of cancer. Tc-99m-DTPA should be applied only in the cases where the benefit expected from the application can meet the potential damage (justification principle) and so that the radioactivity amount to be applied is the lowest dose possible to provide the result expected from the application (as low as reasonably achievable) as in the application of all radiopharmaceuticals.

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 the national reporting system.

### 4.9 Overdose
No symptom related to overdose administration was reported.
However, the bladder should be discharged by giving plenty of liquid and diuretics to patient when it is required to apply over radiation dose due to Tc-99m-DTPA administration.

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical
ATC Code: V09CA01

A pharmacodynamic effect is not expected depending on the radioactive concentration of Tc-99m-DTPA.

### 5.2 Pharmacokinetic properties

**General properties**
MON.DTPA KIT is produced as a sterile and non-pyrogenic lyophilized powder. The solution obtained after being labelled with Technetium-99m as in-vitro is radioactive and is used in the analysis of the functional renal pathologies by intravenous injection and in the imaging of the pathologies disrupting the blood-brain barrier.

Absorption:
The images taken few minutes after the administration show the vascular pool in kidneys. The next images show the radioactivity in urine and renal pelvis taken from both collection systems.
Tc-99m-DTPA is localized also in intracranial lesions and in brain tissue in the cases where the blood-brain barrier is disrupted (such as brain tumors).

Distribution:
After the intravenous injection, Tc-99m-DTPA is rapidly distributed in extracellular fluids. The amount of the dose applied at the ratios varying between 3%- 10% binds to serum proteins.

Elimination:
It is eliminated by glomerular filtration.
Tc-99m DTPA application provides useful information in the determination of the glomerular filtration rate (GFR), but the filtration rate measured occurs lower than the inuline application because it binds to protein at various ratios.

### 5.3 Preclinical safety data
The long-term animal studies examining the carcinogenic and mutagenic effects are not available in the literature. Tc-99m-DTPA kit (Tc-99m-Pentetate) was approved by FDA on 14.02.1974 and has been used from that date.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients
Stannous (II) chloride dihydrate
Sodium hydroxide
Hydrochloric acid
Sodium chloride (0.9 % NaCl)

### 6.2 Incompatibilities
The oxidant substances that Tc-99m-sodium pertechnetate solution might contain cause adverse effect in the labelling processes.
Therefore, it is required not to ventilate into the vial during the process.

### 6.3 Shelf life
Shelf life for MON.DTPA KIT: 24 months at 2-8 $^{0}$C in refrigerator and protected from light.

Shelf life after labelling with radionuclide: The shelf life after labelling with Tc-99m (Tc-99m-DTPA radiopharmaceutical product) is 8 hours from the time of labelling in lead shield, below 25 °C at room temperature and protected from light.

### 6.4 Special precautions for storage
MON.DTPA Kit should be stored at 2-8 ºC in its original package and protected from light. The kit labelled with Tc-99m (Tc-99m-DTPA radiopharmaceutical product) should be stored inside a lead shield below 25 °C at room temperature and protected from light.

### 6.5 Nature and content of container

Type I borosilicate glass vial with bromobutyl stopper and aluminum flip-off cap inside cardboard box.
5 vials/ box

### 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

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

The administration of radiopharmaceuticals creates risks for other persons from externalradiation or contamination from spill of urine, vomiting etc. Radiation protection precautions in accordance with national regulations must therefore be taken.

## 7. MARKETING AUTHORISATION HOLDER

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## 8. MARKETING AUTHORISATION NUMBER(S)

229 / 54

## 9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorization: 10. 02. 2011
Date of last renewal :-

## 10. DATE OF REVISION OF THE TEXT

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## 11. DOSIMETRY

The radiation doses of Tc-99m-DTPA estimated for adults and children are given in the following table. In the calculations, the effective half life was considered as physical half life.

**Estimated Radiation Dose Equivalent (mSv/MBq)**

| ORGAN | Newborn | Child | | | | Adult |
|---|---|---|---|---|---|---|
| | | 1 year | 5 years | 10 years | 15 years | |
| Kidneys | 0.057 | 0.024 | 0.014 | 0.0095 | 0.0069 | 0.0057 |
| Ovaries | 0.026 | 0.012 | 0.0091 | 0.0061 | 0.0069 | 0.0055 |
| Bone surface | 0.027 | 0.013 | 0.0075 | 0.0052 | 0.0040 | 0.0033 |
| Red bone marrow | 0.019 | 0.0084 | 0.0050 | 0.0034 | 0.0027 | 0.0022 |
| Testicles | 0.022 | 0.010 | 0.0077 | 0.0049 | 0.0052 | 0.0038 |
| Bladder wall | 0.19 | 0.079 | 0.086 | 0.058 | 0.097 | 0.077 |
| Effective dose equivalent | 0.034 | 0.015 | 0.012 | 0.0081 | 0.010 | 0.0082 |

***Ref:*** *Radiation Dose Estimates to Adults and Children from Various Radiopharmaceuticals Latest Revision Date: 4/30/96 Radiation Internal Dose Information Center. Oak Ridge Institute for Science and Education . Oak Ridge, TN 37831*

## 12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMEUTICALS

MON.DTPA Kit is not radioactive prior to addition of Tc-99m-sodium pertechnetate solution. The solution prepared after adding Tc-99m is radioactive and should be necessarily kept in a suitable lead container and below 25˚C at room temperature and protected from light.
The unused parts and the wastes occurring after usage should be evaluated within the scope of local requirements for radioactive material.

### Preparation of Tc-99m-DTPA

The preparation of Tc-99m-DTPA solution by using MON.DTPA KIT should be performed behind an appropriate shielding for radiation protection and under aseptic conditions.

Procedure:
- Before starting the process, the kit vial should be checked. The broken, cracked vialor the vial with impaired cover seal should not be used.
- Plastic sterile gloves should be used throughout procedure.
- The cover on the vial is removed, the rubber stopper is wiped with 70% isopropyl alcohol and the vial is placed into the lead container.
- 2-5 ml sterile, non-pyrogenic sodium pertechnetate solution is added into the vial by using lead shielded sterile injector. The product vial was closed under nitrogen gas and

a sterile needle is pricked into the vial before adding pertechnetate in order to compensate the pressure of the vial.
- The maximum Tc-99m activity recommended for labelling the content of a vial is 500 mCi (18500 MBq).
- It is ensured that the lyophilized substance is completely dissolved by slightly shaking the kit vial inside the lead container.
- It is checked whether the solution contains particle or not, whether it is clear or not. The solutions that are not transparent should not be used.
- The amount of radioactivity is determined by measuring in the dose calibrator.

**The kit vial contains nitrogen in order to prevent oxidation. It should be taken care not to ventilate into the vial while taking the administration doses**.

- The shelf life of Tc-99m-DTPA solution is 8 hours. It should be stored inside a lead shield below 25 °C at room temperature and protected from light until the expiration date.

**Determination of radiochemical purity**
*Warning: The study should be carried out in consideration of the operating conditions for radiation safety!*

1. Determination of Tc-99m impurity in the form of colloidal:

Constant phase: Silica gel impregnated TLC layer
Mobile phase: 0.9% sodium chloride
Process steps:
- The chromatography tank and layer are prepared.
- The sample (5-10 µL) is dropped onto the starting point.
- The layer is immediately placed into the tank before the drop is dried and the chromatography is initiated.
- It is developed 10 cm from the dropping point and the plate is taken out of the tank and dried in the air.
- The radioactivity dispersion is determined by using TLC scanner device.

Rf for colloidal Tc-99m peak: 0.0
Rf for Tc-99m–DTPA and sodium pertechnetate peaks: 0,9-1

2. Determination of Pertechnetate impurity

Constant phase: Silica gel impregnated TLC layer
Mobile phase: Methyl-Ethyl-Ketone
- The plate and sample application is repeated as described above. After the Sample drop is dried, the plate is placed into the tank prepared with methyl-ethyl-ketone (MEK) and is developed 10 cm.
- The plate is taken out of the plate and dried.
- Rf values and the activity dispersion are determined by using TLC scanner device.
  Rf for Pertechnetate ($Tc\text{-}99mO_4^-$): 0,9-1.0
  Rf for Tc-99m-DTPA and colloidal form: 0.0

CONCLUSION: Purity % value is calculated from the peak areas. The total of the impurities obtained from both chromatograms should not be more than 5 %.

***CAUTION: After MON.DTPA KIT is labelled with Tc-99m sodium pertechnetate, please stick specially prepared labels included in the cardboard box preferably onto the lead container after completing the information or onto the vial before labelling in order to identify Tc-99m-DTPA solution.***

***The box includes swab for the disinfection of the rubber stoppers of the vial. Please use this swab when preparing the vial for use. The swabs contain 70% isopropyl alcohol. Please do not use an antiseptic agent except for the antiseptic used in the swab.***