SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MON.MDP KIT 10.0 mg lyophilized powder for I.V. injection in a vial

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active ingredient:
Methylenediphosphonic acid (MDP): 10 mg.

Excipients:
0.9% Sodium chloride (sufficient quantity for 1 mL)
Sodium hydroxide (sufficient quantity for pH:5.5)

There is no radioisotope substance in the formulation of MON.MDP KIT.

See section 6.1 for a full list of excipients.

3. PHARMACEUTICAL FORM

Sterile, non-pyrogenic, lyophilized powder

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

MON.MDP KIT is only for diagnostic use. Upon labelling with Tc-99m, it is used as an imaging agent in examination of the bone diseases.

MON MDP KIT is used as a bone imaging agent in recognition of the osteogenesis regions which differ. It is effective in imaging of the alterations shown by the bone metabolism against cases such as infection, trauma, inflammation, infiltration, tumor, or arthropathy. It is indicated in examination of the diseases such as

- Osseous metastases,
- Osteoid osteoma, Fibrous dysplasia, Paget's disease ,
- Osteomyelitis,
- Trauma (stress fracture, osteochondritis),
- Metabolic bone disorders (osteomalacia, osteoporosis) and
- Arthropathy.

4.2 Posology and method of administration

Posology
Recommended dose for adults is 370-740 MBq Tc-99m activity for a patient of 70 kg (10-20 mCi).

Administration frequency and time
It should be administered slowly for 30 seconds with intravenous injection. Optimum imaging time is 1 hour to 4 hours following the injection.

Method of administration
MON.MDP KIT is sterile, non-pyrogenic and lyophilized powder. It is administered intravenously after in-vitro radioactive labelling with Tc-99m.

Immediately before the administration, it is useful to measure the patient dose with a different radioactivity calibration system.

Additional information on special populations

Renal/hepatic impairment
There is no special condition for use. However, the image quality may be affected by the kidney function disorder or obesity.

Paediatric population
Efficiency and safety of the drug for the paediatric patients are not determined yet.

Geriatric population
There is no special condition for use. However, the image quality may be affected in the elderly.

4.3 Contraindications
It is contraindicated for those who are hypersensitive to the technetium Tc-99m medronate or any of the excipients.

4.4 Special warnings and precautions for use
RADIOPHARMACEUTICALS SHOULD BE ADMINISTERED ONLY BY NUCLEAR MEDICINE PHYSICIANS IN NUCLEAR MEDICINE CENTERS.

Use of the technetium Tc-99m medronate may lead life-threatening anaphylactic/ anaphylactoid reactions showing shock, hypotension, loss of consciousness, respiratory distress, hepatization, stertorous respiration, generalized eruption or itching symptoms. Therefore, advanced life support equipment and trained personnel must be kept available during administration.

Phosphonate compounds complex with the cations such as calcium. Therefore, it should be used carefully in the patients who have or are prone to hypocalcemia (alkalosis). Since no hypocalcemia case is reported, the clinical importance of this information is not known. The image quality may be affected by obesity, advanced age or kidney function disorder. (See: 4.2)

Abnormal involvement of the radioactivity indicates existence of a pathologic case. However, advanced examination is necessary to distinguish the benign lesions from the malign lesions.

It is stated in the reports that there is deterioration in the brain scans with Tc-99m technetium pertechnetate when a bone scanning is performed firstly with the agents containing stannous ions. Such deteriorations may cause wrong positive or wrong negative results in the brain scans. Therefore, it is recommended to perform the brain scans prior to the bone imaging. Alternatively, a brain imaging agent such as Tc-99m pentetate may be kept available.

The content of MON.MDP KIT is not radioactive before labelling. The content of the kit vial is used for preparing Tc-99m-MDP 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.

This medicinal product contains sodium less than 23 mg in a vial; in other words, it is mainly “sodium-free”.

4.5 Interaction with other medicinal products and other forms of interaction

In application:

- Antacids (stomach medicines) containing aluminium causes involvement in the liver.
- Estrogens causes involvement in the breast tissue.
- Sodium diatrizoate causes increase in renal and hepatic involvement.
- Iron salts causes increase in intravascular activity.
- E-amino caproic acid causes involvement of the radiopharmaceutical in the muscle tissue.
- Dextrose, cortisone and nifedipine decreases the involvement of the radiopharmaceutical in the bone tissue and affects the examination in the Tc-99m-MDP scintigraphy.
- Cytotoxic cancer chemotherapy causes “Sickle Sign” finding (increased activity distribution around the calvarium) in the scintigraphy.

Additional information on special population

Paediatric population
No drug interaction evaluation is carried out to date.

Renal/hepatic impairment
No drug interaction evaluation is carried out to date.

4.6 Pregnancy and lactation

General recommendation
Pregnancy category: C

Women of childbearing potential / Contraception
Effects of Tc-99m-MDP on the fertility are not known.

The animal studies are not sufficient in terms of the effects on the pregnancy / and-or / embryonic / fetal development / and-or/ birth/ and-or/ postpartum development (See the section 5.3). No potential risk for the humans is known.

For the women in reproductive age group which the administration of radioactive medicinal product is obligatory, the pregnancy should be absolutely examined. The women with delayed menstruation period should be deemed as pregnant unless otherwise is proved. If pregnancy is suspected and has not been proved, the dose necessary for achieving the required clinical information should be adjusted so that the radiation exposure will be minimum. If it does not change the diagnosis, the methods in which the techniques emitting ionized radiation are not used should be preferred as an alternative.

The optimum administration period for the women with child-bearing capacity is 10 days following completion of menstruation.

Pregnancy period
There is no sufficient data on use of MON.MDP KIT in the pregnant women.

MON.MDP KIT should not be used in the pregnancy period unless it is necessary (when the expected benefit from Tc-99m-MDP is higher than its potential damage.
In such cases, the doctor should be very careful and administer the lowest possible activity dose.

Lactation
The Tc-99m pertechnetate passes to the breast milk. Therefore, if this medicine is necessary during the breast-feeding period, do not breast-feed at least for 12 hours after using the medicine. Feed the baby using any other feeding method (baby formula, etc.). Dispose the

milked during this period. In addition, avoid contact with the baby during this 12 hours period for protection from radiation.

Fertility
Effect of Tc-99m-MDP on fertility is not known.

4.7 Effects on ability to drive and use machines
Administration of Tc-99m-MDP has no negative effect on ability to drive and use machines.

4.8 Undesirable effects
The undesirable effects are listed by the following frequency degrees.
Very common (> 1/10); common (≥1/100 to <1/10); uncommon (≥1/1000 to < 1/100); rare (≥1/10.000 to < 1/1000); very rare (<1/10.000); unknown.

The side effects related to the administration of Tc-99m-MDP as reported in the literature are given below.

Nervous system diseases	Shivering, dizziness (rare)
Vascular diseases	Hypotension
Gastrointestinal diseases	Nausea, vomiting
Skin and subcutaneous tissue diseases	Itching, skin eruption
Musculoskeletal disorders, connective tissue and bone diseases	Edema and/or arthralgia in hands or feet
General disorders	Fatigue (rare)

Advanced life support equipment and trained personnel must be kept available against life-threatening anaphylactic/ anaphylactoid reactions (shock, hypotension, loss of consciousness, respiratory distress, hepatization, stertorous respiration, generalized eruption or itching).

Since such reactions are reported voluntarily from a population with an uncertain size, it is not always possible to determine their frequency or causal relationship arising from exposure to the drug.

Exposure to the ionized radiation may induce cancer formation. As for all radiopharmaceutical administrations, Tc-99m-MDP should be administered only if the expected benefit is higher than the potential damage (justification principle) and in such a manner that the amount of radioactivity to be implemented will be as low as reasonably achievable for the result expected from the administration.

4.9 Overdose

No symptom is reported about overdose.
However, in the case of overdosed radiation due to the administration of Tc-99m-MDP, a diuretic should be administered and the bladder should be emptied.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group : Diagnostic radiopharmaceutical
ATC code : V09BA02

No pharmacodynamic activity is expected since it is administered at low concentration.

5.2 Pharmacokinetic properties

General properties
MON.MDP KIT is manufactured as sterile and nonpyrogenic powder. The solution obtained upon in-vitro marking with Technetium-99m is radioactive and used as a bone imaging agent by intravenous injection.

Absorption :
Upon administered intravenously, Tc-99m-MDP is rapidly isolated from the blood.

Distribution and Biotransformation:
Approximately 50% of each dose injected is involved in the bones, and the remaining amount is excreted by urine within 24 hours. Minimum involvement has been observed in the soft tissue organs, particularly the liver.

Approximately 40-50 % of each dose is involved in the bones within 3 hours. The complex is rapidly isolated from the blood and approximately 50% of each dose is cleared by urinary excretion within the first 3-6 hours.

Involvement in the bones arises as a function of the bone activity at extraction of the complex, and blood flow to the bone. The bone mineral crystals are generally considered as hydroxyapatite, and the complex seems to have an affinity for the hydroxyapatite crystals in the bone.

Elimination :
Radioactivity is isolated from the blood very rapidly. The blood isolation curve is an exponential curve with 3 components. 10% of the injected dose remains in the circulation for 1 hour after injection, 5% for 2 hours, and only 1% for 24 hours.

Rapid isolation from the blood allows for early image capturing due to the high involvement of bone/soft tissue.

5.3 Preclinical safety data

No long-term animal study for the carcinogenic and mutagenic effects is available in the literature.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Stannous (II) chloride dihydrate
Gentisic acid
0.9% sodium chloride solution
Sodium hydroxide
Hydrochloric acid

6.2 Incompatibilities

The oxidizing agents that may exist in the Tc-99m sodium pertechnetate solution have a negative effect on the labelling operations.
Therefore, no air should be given in the vial during the operation.

6.3 Shelf life

MON.MDP KIT: 12 months

The product labelled with the Tc-99m sodium pertechnetate (^{99m}Tc-MDP): 8 hours

6.4 Special precautions for storage

Lyophilized powder should be kept in the refrigerator at 2-8 °C with protection from light.
The product labelled with the Tc-99m sodium pertechnetate (^{99m}Tc-MDP) should be kept in its lead shield at a room temperature under 25 °C with protection from light and used in 8 hours.

6.5 Nature and content of container

Type I colourless glass vial with bromobutyl stopper and aluminium flip-off cap within a 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

Eczacıbaşı Monrol Nükleer Ürünler Sanayi ve Ticaret A.Ş.
TÜBİTAK MAM Teknoparkı
41470 Gebze Kocaeli TURKEY
Tel: +90 262 648 02 00
Fax: +90 262 646 40 39
E-mail: monrol@monrol.com

8. MARKETING AUTHORISATION NUMBER

243 / 77

9. DATE OF FIRST AUTHORISATION / RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.07.2012
Date of last renewal: -

10. DATE OF REVISION OF THE TEXT

-

11. DOSIMETRY

Physical Characteristics:
The Technetium (^{99m}Tc) pertechnetate solution is obtained from the Mo99/Tc99m generator and decayed by isometric transition. Its half life is 6.02 hours. The main photon and properties used in the scanning and imaging studies are given in the Table 1.

Table-1: Emitted background radiation*

Radiation	Decay / % average	Average Energy (keV)
Gamma-2	89.07	140.5

*Kocher, David C., "Radioactive Decay Data Tables" DOE/TIC-11026, p. 108, (1981)

External radiation**:**
The specific gamma-ray constant for ^{99m}Tc is 0.78 R/mCi/h at 1 cm. The necessary lead thickness for halving the radiation value is 0.017 cm for the first half value. The Table-2 gives the various lead thicknesses for the attenuation degrees of the rays.

Table-2: Radiation attenuated by lead shielding

Thickness of lead shield (cm)	Attenuation coefficient
0.017	0.5
0.08	10-1
0.16	10-2
0.25	10-3
0.33	10-4

The coefficient table used to calculate the activity remaining in the specified periods after the calibration hour is given below.

Table-3: Physical Decay Table: Tc-99m, half-life: 6.02 hours

Hour	Calculation Coefficient	Hour	Calculation Coefficient
0*	1.000	5	0.562
1	0.891	6	0.501
2	0.794	8	0.398
3	0.708	10	0.316
4	0.631	12	0.251

* Calibration hour

In the calculations, the effective half life is considered as the physical half life.
The following table gives the radiation doses anticipated to be involved in the tissues and organs upon intravenously administration of maximum 740 MBq (20 mCi) of Tc-99m-MDP to an adult (70 kg) patient.

Table-4: Absorbed Radiation Dose*:

ORGAN	mGy/ 740 MBq	rads/20 mCi
Whole body	1,3	0.13
Whole bone	7.0	0.70
Red bone marrow	5.6	0.56
Kidneys	8.0	0.80
Liver	0.6	0.06
Bladder wall		
Urinating in 2 hours	26.0	2.60
Urinating in 4,8 hours	62.0	6.20
Ovary		
Urinating in 2 hours	2.4	0.24
Urinating in 4,8 hours	3.4	0.34
Testicles		
Urinating in 2 hours	1.6	0.16
Urinating in 4 hours	2.2	0.22

*Calculation Method: "S" Absorbed Dose per Unit Cumulated Activity Selected Radionuclides and Organs, MIRD Pamphlet No. 11, 1975.

The dose exposed by a patient administered with maximum 740 MBq (20 mCi) of Tc-99m technetium for a whole body scan is 0.2 μSv, 0.02 mR[1] dır.

1: Barrall, R.C., Smith, S.J., Personnel Radiation Exposure and Protection from 99m Tc Radiations, In: Kereiakes, J. G., Corey, K. R., eds. Biophysical Aspects of the Medical Use of Technetium Tc99m, American Association of Physicists in Medicine Monograph No. 1, 1976: p. 77.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMEUTICALS

The content of MON.MDP KIT is not radioactive before addition of the Tc-99m sodium pertechnetate solution. Upon addition of Tc-99m, the vial must be kept in an appropriate lead shield and at room temperature below 25˚C.

MON.MDP KIT is sterile and non-pyrogenic. Labelling operations with the Technetium Tc-99m sodium pertechnetate must be carried out under the aseptic conditions and behind a lead shield.

The bonding reaction between the kit content and Tc-99m radionuclide is depending on the amount of the +2-valency stannous ion in the kit. Therefore, no sodium pertechnetate solutions containing any oxidizing agent must be used in the marking operation.

Content of the vial may not be directly administered to the patient before marked with the Technetium Tc-99m sodium pertechnetate.

As with the other radioactive products, appropriate safety precautions must be taken in order to prevent unnecessary exposure of the clinic staff and other persons to the radiation.

Preparation of ^{99m}Tc-MDP:

- Plastic sterile gloves should be worn during the operations.
- The kit vials should be checked before the operation. Broken or cracked vials or vials with broken cap seal must not be used.
- Remove the cap of the vial and mop the rubber stopper with the alcohol swabs included in the container, and then, place the vial in the protective lead shield.
- Adhere the solution label within the cardboard box to the lead shield.
- Since the product vial is sealed under the nitrogen gas, stick a sterile needle to the vial cap in order to equalize the vial pressure.
- Add 2-5 ml of sterile, non-pyrogenic Tc-99m-sodium pertechnetate solution to the vial using the lead-shielded, sterile injector. Maximum recommended Tc-99m activity is 500 mCi.
- Slowly shake the kit vial in the lead shield with the cap closed to ensure that the lyophilized powder is completely dissolved, and then wait 1-2 minutes.
- Check if the solution contains any particle and if the solution is clear under the fume hood and behind a lead shield. If the solution is blur or discoloured, it should not be used.
- Write the preparation date and time, volume, activity of the solution, and name of the preparer on the solution label on the lead shield.

- Keep the ^{99m}Tc-MDP solution at a room temperature below 25 ºC and dispose of the remaining part which is not used after 8 hours.
- Before use, take a measurement in the doze calibrator and determine the radioactivity amount.

The kit vial contains nitrogen in order to prevent oxidation. It should be taken care not to give air in the vial while drawing the administration doses.

Determination of radiochemical purity:
Warning: The study should be carried out under the radiation safety working condition!

1. Determination of the purity of Tc-99m in the colloidal form:
Stationary phase: Silica-gel impregnated TLC plate (ITLC-SG)

Mobile phase: Sodium acetate solution (136 g/l)
The ITLC-SG plate is activated by heating at 110°C for 10 minutes.
The chromatography tank is prepared using the aforementioned solvent system.
The sample is dropped to the start (0) line, and placed in the chromatography tank before the drop is dried.
It is moved 10 cm from the dropping point, and the plate is removed from the tank and allowed to be dried in the air.
The Rf values and activity distribution are determined using the TLC scanner.
For Hydrolyzed technetium and colloidal form, Rf= 0
For Tc-99m-medronate and Sodium pertechnetate, Rf=0.9-1

2. Determination of the impurity of sodium pertechnetate:
Stationary phase: Silica-gel impregnated TLC plate (ITLC-SG)
Mobile phase: Methyl-Ethyl Ketone
1. The chromatography tank and plate is prepared as explained above.
2. The sample is dropped to the start (0) line; and placed in the chromatography tank after it is ensured that the drop is immediately dried.
3. It is moved 10 cm from the dropping point, and the plate is removed from the tank and allowed to be dried in the air.
4. The Rf values and activity distribution are determined using the TLC scanner.
   For Sodium pertechnetate, Rf=0.9-1
   For Tc-99m-medronate and colloidal form, Rf= 0

CONCLUSION: The purity value % is calculated from the peak areas. The impurity of pertechnetate should not be more than 2%, and total impurity from both chromatograms should not be more than 5%.

CAUTION: After MON.MDP 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 ^{99m}Tc-MDP.

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.