



SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

MDP 5 mg powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Composition of MDP powder for injection

<i>Component Active substance</i>	<i>Quantity per vial</i>	<i>Function</i>
Medronic acid (MDP)	5.0 mg	Organ-specific chelating agent of ^{99m} Tc radioisotope

Composition of ^{99m}Tc-MDP radioactive injection

<i>Component Active substance</i>	<i>Quantity per vial</i>	<i>Function</i>
^{99m} Tc-MDP	3.0 – 6.0 GBq	Organ-specific diagnostic information

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Pharmaceutical form of MDP kit: powder for injection
Pharmaceutical form of ^{99m}Tc-MDP: radioactive sterile injection
^{99m}Tc-MDP injection can be prepared in situ at the site of the use ie. at isotope laboratories of clinics or hospitals by mixing MDP powder for injection (lyophilisate in the vial) and [^{99m}Tc]pertechnetate eluate. Sterile, pyrogen free solution of [^{99m}Tc]pertechnetate can be obtained by using ^{99m}Tc/⁹⁹Mo generator.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

This medicinal product is for diagnostic use only.

INDICATION FIELD: ISOTOPE DIAGNOSTICS

For bone scintigraphy (diagnostic skeletal imaging). Use of the preparation is highly recommended for indications listed below:

- Primer bone tumours
- Metastases of other tumours, e.g. prostate cancer, breast cancer, lung cancer
- Osteomyelitis,
- Metabolic bone diseases,
- Paget's disease.

4.2 Posology and method of administration

370-740 MBq ^{99m}Tc-MDP for intravenous administration

^{99m}Tc-MDP obtained in one labelling reaction can be divided to 3 – 6 patient doses.

^{99m}Tc-pertechnetate activity for labelling must be chosen so that individual patient dose should be 370 – 740 MBq (for an average 70 kg bodyweight) at the time of the investigation.

For paediatric examination (see Chapter 4.3.) use Webster's equation to determine the activity to be administered:

$$A_{child} = \frac{[(N + 1) \cdot A_{Adult}]}{N + 7}$$

where N: age of the child [year], A_{child}, A_{adult}: activity [MBq]

Method of examination

^{99m}Tc-MDP is administered intravenously to the patient. Bone scintigraphy, which can be whole body or targeted scan, and SPECT scan, should be performed 2 – 4 hours after administration. Imaging with gamma camera or scanner should be performed after administration.

and method of further treatment should be concluded based on these results. The table of Chapter 11 contains absorbed radiation dose data in µGy in case of intravenous administration of 1 MBq of ^{99m}Tc-MDP. Multiply these specific absorbed radiation dose data by the effectively administered activity (in MBq) to obtain the required absorbed radiation dose data in µGy.

According to the recommendations, quantity of ^{99m}Tc-MDP administered to one patient is not less than 0.83 mg and not more than 1.67 mg. If the whole content of the vial containing the labelled substance is administered to one patient by mistake, 5 mg of ^{99m}Tc-MDP is introduced in the body which may correspond to 0.0714 mg/kg in case of 70 kg body weight.

Acute toxicity studies on mice showed no clinical symptoms, if less than 9 mg/kg of bodyweight is administered. Therefore appearance of clinical symptoms is not expected even if the whole content of the vial containing the labelled substance (5 mg of ^{99m}Tc-MDP which represents 0.0714 mg/kg of bodyweight level calculated on 70 kg average bodyweight) is administered to one patient by mistake. This is equivalent to 0.8 % of the no observed effect level. Thus, no toxic effects are expected in case of overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Diagnostic radiopharmaceutical, ATC code: V09B A 02

Behaviour of ^{99m}Tc-MDP after intravenous administration is similar to that of other diphosphonates labelled with ^{99m}Tc isotope (e.g. hydroxymethylenediphosphonate and 1-hydroxyethylidene-1,1-diphosphonate). After ^{99m}Tc-MDP is rapidly cleared from the blood it is accumulated mainly by the skeletal system. The soft tissues uptake ^{99m}Tc-MDP in negligible quantities. Mechanisms of the uptake are ion exchange and chemisorption in the inorganic matrix of the bone, in ionic hydroxyapatite (Ca₁₀(PO₄)₆(OH)₂). Phosphate groups of the surface of the bone matrix react with the free PO₃H₂ groups of the MDP coordinated to technetium. Thus, this ion exchange reaction results in the adsorption of the ^{99m}Tc – activity on the bone matrix. This process occurs in the healthy bone, but accumulation is higher at sites which are characterised by the increased bloodstream and increased ossific activity (osteoblast function).

Therefore, in bone lesions, which are primer tumours, metastases, bone fissures, fractures and inflammation, higher activity of ^{99m}Tc -MDP can be found. This increased activity provides excellent possibility for nuclear imaging.

Significantly smaller quantity of the administered ^{99m}Tc -MDP binds to the proteins of the blood plasma, resulting a low whole body background. The non-bound percentage of the radiopharmaceutical preparation is excreted via the urine; excretion via the hepatobiliary system is usually negligible.

Generally 50 per cent, in healthy humans not more than 31 per cent of the administered dose is accumulated in the bones. In bone metastases 40 per cent of the activity of the administered ^{99m}Tc -MDP is accumulated in the bone metastases and only metastases accumulates the substance at these sites. Therefore, bone metastases are highlighted on the images of the skeleton. The same is true for fractures, inflammations, hyperparathyroidism and osteoporosis. General principle of isotope diagnostic imaging is that the radioactive tracer must not have influence on the tracing system, e.g. the physiological processes of the human body. In the present case this means that the radioactive tracer must not have effect or it can have only negligible influence on the ossific processes. If the administration of the preparation is performed according the recommendations, the criteria above is fulfilled, since not less than 0.83 mg and not more than 1.67 mg of ^{99m}Tc -MDP is administered to a patient. Pharmaceutical or pharmacodynamic effects of such small quantities can not be observed.

5.2 Pharmacokinetic properties

Intravenously administered ^{99m}Tc-MDP is cleared from the blood in three steps:

1. rapid phase, T_{1/2} = 3.5 min,
2. moderate phase, T_{1/2} = 27 min,
3. slow phase, T_{1/2} = 144 min.

In the rapid phase, ^{99m}Tc-MDP is cleared from the blood to the extravascular area. The moderate phase is equivalent to the uptake process by the bone. In the slow phase, the dissociation of ^{99m}Tc-MDP bounded to the plasma proteins reaches its highest value and remains constant for further 72 hours.

^{99m}Tc-MDP is excreted via the urine. The highest activity in the kidneys appears at 20 minutes after administration. In case of normal renal function, 32 % of the total administered activity is filtered glomerularly. 47% of the

glomerularly filtered portion is present in the urine 2 hours, and 60% in 6 hours after administration. Activity showing up in the liver and in the intestines is not significant.

5.3 Preclinical safety data

Acute toxicity studies on mice showed no clinical symptoms, if less than 9 mg/kg of bodyweight is administered. If administration complies with the recommendations, quantity of ^{99m}Tc-MDP administered to one patient is not less than 0.83 mg and not more than 1.67 mg. If the whole content of the vial (containing the labelled substance) is administered to one patient by mistake, 5 mg of ^{99m}Tc-MDP is introduced in the body which represents 0.0714 mg/kg of bodyweight level (calculated on 70 kg average bodyweight). This is equivalent to 0.8 % of the no observed effect level. Thus, no toxic effects are expected in case of overdose. Further advantage of the product is that the activity of [^{99m}Tc]pertechnetate, which is in the range of 3 – 6 GBq, does not affect the radiochemical purity of the preparation. Quantity of radiochemical impurities is always less than 10 %, therefore the kit is safe also from the point of view of labelling.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

<i>Component</i>	<i>Quantity per vial</i>	<i>Function</i>
Stannous chloride dihydrate	0.6 mg	Reducing agent of [^{99m} Tc]pertechnetate
Ascorbic acid	0.5 mg	Stabiliser
Urea	10.0 mg	Filler

6.2 Incompatibilities

One component of MDP kit is stannous chloride, which is a reducing agent. It reduces free pertechnetate (+7 oxidation state) to +4 oxidation state, in which technetium readily forms complex with MDP. It is important to keep away the content of the vials from moisture and oxidising agents, for example chemical oxidation agents or oxygen of the air. Alkaline media facilitate the oxidation of Sn(II) before the labelling reaction, this is why the product is incompatible with bases. As a result of these incompatibilities it is recommended to remove the closure of the closed injection vials just right before the labelling reaction. Perform the labelling according to the instructions detailed in Section 12.

6.3 Shelf life

Shelf life of MDP kit is 12 months from the day of production, indicated on the labels.

One box contains 6 vials. Labelling of the contents of vials can be performed at different times (within the expiry date, stated on the labels.) The ^{99m}Tc-MDP injection should be used within 3 hours after labelling.

6.4 Special precautions for storage

Store MDP kit in refrigerator (2 - 8°C).

Do not store ^{99m}Tc-MDP injection above 25°C. Comply with the regulations for radiation safety.

6.5 Nature and contents of container

The injection vials of MDP kit contain the sterile, pyrogen-free and freeze-dried components. The labelled BEKA type 6 ml injection vials are closed with rubber stopper and tear-off kombicap (aluminium and plastic). One box contains six vials, one Summary Of Product Characteristic and Patient Information Leaflet and six labels with radioactive material sign. The box is wrapped in shrinkmg foil.

6.6 Special precautions for disposal and other handling

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

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER(S) OGYI-T-9702/01

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19 May 1992 / 17 December 2009

10. DATE OF REVISION OF THE TEXT

17 December 2009

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11. DOSIMETRY

Individual patient dose is 370–740 MBq. Estimated absorbed dose values of 1 MBq of the injection for an average body weight of 70 kg are given in the table below.

Organ	Absorbed dose [μGy / MBq]	dose
Skeleton	12.2	
Bone marrow	2.7	
Kidneys	1.6	
Bladder	13.3	
Whole body	2.7	

Radiation physical properties of ^{99m}Tc-MDP are as follows:

Physical half-life 6 hours

Energy and intensity of the emitted 140 keV 100 %

gamma photons

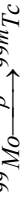
Energy and intensity of the emitted –

beta particles

During the decay ⁹⁹Tc is produced.

^{99m}Tc isotope is produced in the ⁹⁹Mo generator by β-decay via the next

reaction:



Secondary product of the reaction is ⁹⁹Tc radioisotope, which is produced owing to the short half-life of ^{99m}Tc in quantity less than 0.1%.

12. INSTRUCTIONS FOR PREPARATION OF RADIOPHARMACEUTICALS

Remove the protective foil and lift up the upper part of the paper box to access the vials. MDP kit can only be administered to patient after labelling it with ^{99m}Tc.

Never administer MDP kit without performing the labelling. Never administer MDP in vivo kit or its components to patients, only the ^{99m}Tc-MDP injection is allowed for human use.

^{99m}Tc-MDP solution contains radioactive isotope. For handling, shipping and storage of this product the rules and regulations referring to the radioactive materials should be observed.

Labelling procedure

Place the vial which contains the freeze-dried powder in a small lead container with a wall thickness of 3 mm. Under aseptic circumstances inject 3 – 6 GBq of sterile sodium pertechnetate into the vial through the rubber stopper with a sterile syringe. Volume of the sodium pertechnetate solution should be not less than 2 ml and not more than 5 ml. If it is necessary, use saline for dilution. Shake well. Incubate the vial at room temperature for 15 minutes. Now the labelled substance (^{99m}Tc-MDP) can be intravenously administered. pH of the labelled solution is in the range of pH = 5.0 – 7.0.

Utilize the labelled solution in 3 hours. Over this period the percentage of radiochemical impurities should not be more than 10%.

Control of the drug product
Radiochemical purity of ^{99m}Tc-MDP is tested by using paper chromatography and thin layer chromatography.

Determination of free ^{99m}TcO₄⁻ by paper chromatography

skeletal system and bone lesions become visible. After administration of the injection, you have to drink approximately 1 L of water.

As the medicine contains gamma-radiator radioactive isotope, it can be detected from outside the body using gamma cameras. The pictures taken by this camera show the distribution of the radioactive isotope in your body and organs. The pictures can give your doctor valuable information about the structure and working of the organ helping this way to choose the best treatment.

This medicine is for diagnostic use only.

2. BEFORE YOU USE MDP

Do not use MDP

- if you are allergic (hypersensitive) to the active substance or any of the other ingredients of MDP.
- If you are pregnant or breastfeeding, except if your doctor decides otherwise
- If you are under 18 years of age, except if your doctor decides otherwise

Make sure you carry out the doctor's instructions both before and after the examination in order to avoid radioactive exposure of other people and the radioactive contamination of the environment.

The radioactive isotope is excreted in the urine, faeces, sweat and other secretions temporarily contaminating the environment this way.

Using other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

No interactions with other medicines are known.

Using MDP with food and drink

You can take MDP with any food or drink.

Pregnancy and breastfeeding

It is important to tell your doctor if there is any possibility that you are pregnant or breastfeeding.

In these cases your doctor will consider the necessity of the radioisotope diagnostics. The radioisotope can be dangerous to the foetus and the infant, and it is excreted in breast milk. Therefore, it is possible that your doctor will choose other, non-radioactive method. Trust your doctor, because the decision will be made in accordance with strict regulations.

If you are breastfeeding and you will be examined with this product, you should stop breastfeeding for the period recommended by your doctor. During this time the radioactive isotope will be eliminated from your body. Use formula feed for your child. The breast milk should be expressed and collected and spilled out after dilution. You can restart breastfeeding when the radiation dose for the child is less than 1 mSv. Your doctor will decide about the restarting.

Driving and using machines

^{99m}Tc-MDP has no influence on the ability to drive and use machines.

Important information about some of the ingredients of MDP

When you are given ^{99m}Tc-MDP you receive a small amount of radiation. The adsorbed dose in this case is usually smaller than those of certain X-ray examinations (e.g. CT). Your doctor will always consider the possible risks and advantages.

If you have any further questions on the use of this medicine, ask your doctor.

3. HOW TO USE MDP

^{99m}Tc-MDP is prepared from MDP kit at the site of utilisation (isotope laboratories of hospitals or clinics) by using ^{99m}Tc-pertechnetate eluate. ^{99m}Tc-MDP is administered intravenously. Amount of the administered activity, method and timing of imaging is decided by your doctor according to the type of examination and your state of health.

What should you do if you received overdose of the medicinal product?

There are strict rules and regulations on handling, use and disposal of radioactive materials. Therefore, ^{99m}Tc-MDP can only be used in hospitals or institutes.

MDP can be handled, used and administered only by people specialized for handling of radioactive materials and waste. These people give you instructions about the precautions and warnings. Comply with their instructions.

Since ^{99m}Tc-MDP is given by a doctor under controlled conditions, the probability of overdose is low. In the unlikely event of overdose your doctor will advise you to drink lots of liquid which will accelerate the elimination of the drug from your body. You should take all necessary precautions against the contamination of your environment with radioactivity. Comply with the instructions given by your doctor. ^{99m}Tc-MDP which is temporarily present in your body and the excreted material loose their radioactivity in a natural way.

If you have any further questions on the use of this medicine, ask your doctor.

4. POSSIBLE SIDE EFFECTS

Like every medicinal product, MDP might cause adverse reactions, but such effects do not appear in every case. If any adverse reaction becomes serious, inform your doctor.

Exposure to ionising radiation is linked with cancer induction and a potential for development of hereditary defects. However these effects are hardly expected regarding the applied amount of activity.

Your doctor will decide the amount of the administered activity considering the radiation exposure and the diagnostic results.

If you have any further questions on the use of this medicine, ask your doctor.

It is important to tell your doctor if you experience any side effect.

5. HOW TO STORE MDP

Keep out of the reach and sight of children and people who are not authorized to handle, use or transport this product!

Hospital staff will ensure that the product is stored correctly and not used after expiry date stated on the label.

MDP powder for injection must be stored in refrigerator at 2-8 °C.

Radioactive ^{99m}Tc-MDP is to be stored below 25°C, considering the regulations for radiation safety.

^{99m}Tc-MDP must be used within 3 hours.

6. FURTHER INFORMATION

What MDP contains

The active substance is 5.0 mg medronic acid (MDP) per vial

Other ingredients are: Stannous chloride dihydrate, Ascorbic acid, Urea

The active substance of the labelled, radioactive MDP: ^{99m}Tc-MDP

What MDP looks like and contents of the pack

The injection vials (BEKA type, 6ml) containing the sterile, pyrogen-free freeze-dried product are closed with rubber stopper and tear-off komicap (aluminium and plastic).

Six vials of MDP kit are packed into one paper box, with six label with radioactive symbol.

Marketing Authorisation Holder and Manufacturer

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