MDP RPHPHARMA

PLEASE READ CAREFULLY BEFORE USING THE PRODUCT.

DRUG FOR DIAGNOSTIC USE IN NUCLEAR MEDICINE.
This product is only for use in specialized clinics and hospitals.

PHARMACEUTICAL FORM AND PRESENTATION
Kit containing 5 vials of lyophilized, sterile and pyrogen-free reagents, sealed under nitrogen atmosphere.

COMPOSITION
Each vial contains:

COMPOSITION	AMOUNT
medronic acid	10.0 mg
para-aminobenzoic acid	2.0 mg
stannous chloride dihydrate	1.2 mg
water for injection	1.1 mL

Table 1- Composition of the MDP kits

1. INDICATIONS
The radiopharmaceutical MDP-Tc-99m is only recommended for diagnostic purposes and is used in bone scintigraphy. Its uses include: locating malignant or benign primary tumors, detecting metastasis, early diagnosis of osteomyelitis, locating fractures undetectable by X-ray (stress fractures), assessing bone pain without significant radiological findings, detecting avascular necrosis, systemic evaluation of patients with osteoarticular disease, among others. MDP-Tc-99m can also be used to detect areas of acute myocardial infarction, assessing its extent and severity.

INTRAVENOUS ADMINISTRATION. ADULT AND PEDIATRIC USE.

2. EFFICACY
In vitro and in rodents assays suggest Tc-99m-MDP accumulates in bones by adsorption and incorporation on hydroxyapatite structure (Heggli et al., 1988; Chopra, 2009).

3. PHARMACOLOGICAL CHARACTERISTICS
When injected intravenously, MDP-Tc-99m is quickly cleared from the bloodstream and moves to bone surfaces, likely due to absorption of hydroxyapatite crystals. Phosphonates complexed with metastable technetium-99 can also accumulate in myocardial infarction through absorption of amorphous calcium phosphate or complexation of denatured proteins and other macromolecules. Three hours after injecting the radiopharmaceutical, total activity in the bloodstream is 3.22 ± 0.269%. The complex is eliminated through kidneys.

4. CONTRAINDICATIONS
There are no reported contraindications.

5. WARNINGS AND PRECAUTIONS
During pregnancy or breastfeeding, this radiopharmaceutical should only be used in cases of extreme necessity, when the risk of exposure of the fetus or newborn to radiation is justified by the importance of diagnosis.
The administration of a radiopharmaceutical during pregnancy can cause mutagenic changes in the fetus.
During lactation, technetium-99m (99m Tc) is excreted in breast milk. Breastfeeding should be suspended for at least 12 hours after injection and the milk produced during this period discarded.
Avoid close contact between mother and baby for the 12 hours following administration of the radiopharmaceutical.
Approximately 1.5 - 3% of MDP-Tc-99m is excreted in milk.

6. DRUGS INTERACTIONS
Several drugs and conditions interfere in the biodistribution of radiopharmaceuticals used in bone studies. The MDP-Tc-99m complex interacts directly or indirectly with compounds containing iron, amphotericin B, gentamicin, cyclophosphamide, vincristine, doxorubicin, aluminum-containing antacids, bisphosphonates, dextrans, vitamin D3, methotrexate, diatrizoic acid, calcium gluconate, heparin, meperidine, estrogen and corticosteroids, potentially compromising image quality.

7. STORAGE PRECAUTIONS
This drug is valid for 12 months from the date of manufacture. Transport at room temperature and store in a cool dark place at temperatures between 2 and 8° C.
When added to the vial of MDP without the presence of air, the sterile pyrogen-free solution of sodium pertechnetate (Na $99mTcO_4$) produces rapid labeling that remains stable *in vitro* for 10 hours.
After complexation with technetium-99m (99m Tc) store in the dark between 2° and 30° C.

Lot number, manufacture and expiration dates: see packaging.
Do not take medicines that has expired.
All medicines should be kept out of reach of children.
Before administering to the patient, take note of the appearance of the product, which should be clear and colorless.

8. DOSAGE AND INSTRUCTIONS FOR USE
Route of administration: intravenous.
Recommended activity for bone scintigraphy is 740-1110 MBq (20-30 mCi), considering a 70 kg adult patient. For pediatric patients the dose should be adjusted according to the child's weight.

8.1. INSTRUCTIONS FOR PREPARATION AND STORAGE AFTER COMPLEXATION
- Use aseptic procedures and take precautions to prevent exposure to radiation.
- Place the vial, previously disinfected with 70% ethyl alcohol, in a lead shield.
- Keep air from entering the vial and remove air bubbles from the syringe before adding the sodium pertechnetate solution.
- Aseptically add 3 to 5 mL of $99mTcO_4^-$ (if needed, top up with 0.9% NaCl) with maximum activity of 12950 MBq (350 mCi) to the vial.
- Without removing the needle, aspirate an equal volume of air to maintain atmospheric pressure within the bottle.
- Place a fitted cover onto the lead shield. – Swirl the vial gently for 30 seconds until the lyophilisate has completely dissolved. The solution should be clear and free of particles.
- Let stand at room temperature for 10 minutes to allow a complete labeling reaction.
- Carry out quality control.
- Following quality control procedures, extract doses in accordance with the patient's body weight, taking care to avoid the entry of air when handling the flask. Use sterile, disposable syringes.

8.2. QUALITY CONTROL - RADIOCHEMICAL
Use two 3mm Whatman plates measuring 6.5 cm long and 1 cm wide, as shown in figure 1. Once the complexation incubation time has elapsed, add a drop of the material on the application line of each of the plates. Place one of the plates in a chromatographic tank containing Butanone PA (PLATE 1) and the other into a chromatographic tank containing a solution of 0.9% NaCl (PLATE 2). Wait until the solvents migrate to the top lines of the plates, which can happen at different times. Remove the plates from the chromatography tanks. Cut PLATE 1 in half and PLATE 2 1.5 cm from the application point. Calculate labeling efficiency using the formula below. Analyze the results of labeling efficiency in accordance with table 2.

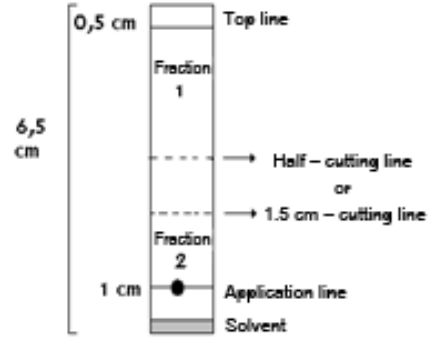

Figure 1 – Cutting the chromatography plates

PLATE 1: % $99mTcO_4^-$:

$$\frac{\text{activity fraction 1}}{\text{ativity fraction 1} + 2}$$

PLATE 2: % $99mTcO_2$:

$$\frac{\text{activity fraction 2}}{\text{ativity fraction 1} + 2} \times 100 \leq 10\%$$

Labeling efficiency /radiochemical purity should be > 85%.

$$\mathbf{100 - (impurity\ plate\ 1 + impurity\ plate\ 2)} > 85\%$$

CHROMATOGRAPHY ANALYSIS OF MDP-Tc-99m			
Chromatography System		**(99m Tc) Species**	
Stationary Phase	**Mobile Phase**	**Origin**	**Front**
PLATE 1	Butanone PA	MDP-99mTc $99mTcO_2$	$99mTcO_4^-$
PLATE 2	0.9% NaCl	$99mTcO_2$	MDP-99mTc $99mTcO_4^-$

Table 2 – Chromatography systems for radiochemical control of MDP-Tc-99m.

8.3. QUALITY CONTROL - pH
Apply a sample of the radiopharmaceutical on the pH indicator strip. Wait 30 seconds and compare the color of the strip against the parameters in this box.
The pH range for the radiopharmaceutical MDP-Tc-99m should be between 4.0 and 7.8.

8.4. PRECAUTIONS ON ADMINISTRATION

This drug becomes radioactive after adding sodium pertechnetate solution. The use of lead shielding, suitable gloves and goggles should be mandatory.
The components of the kits are sterile and pyrogen-free. In order to preserve the sterility of the product, it should be handled in accordance with the Good Practices on Handling Sterile Products (intravenous products).
Precautions should be taken when using ionizing radiation. As such, radioactive waste (used materials, recipients and other waste) should be correctly disposed of in compliance with radiation protection guidelines.

DOSES ADMINISTERED TO CHILDREN AND ELDERLY SHOULD BE CALCULATED ACCORDING TO THE BODY SURFACE AREA

8.5. TOXICITY TESTS

Toxicity is not an issue when considering the design and development of radiopharmaceuticals due to the small amount used, which does not produce a pharmacological response.

8.6. PHYSICAL CHARACTERISTICS OF METASTABLE TECHNETIUM-99M

Tecnetium-99m (99m Tc) has the ideal physical properties for studying scintigraphic images.
99m Tc decays into technetium-99 through isomeric transition and has a physical half-life of 6.02 hours.

RADIATION	AVERAGE/DECAY (5)	AVERAGE ENERGY (keV)
Gama -2	89.07	140.5

Table 3 – Data on the main radiation emitted
'Kocher, David C., "Radioactive Decay Data Tables," DOE/ TIC-11026. 108(1981).

8.7. DOSAGE

Estimated absorbed radiation doses for the total body and selected organs are listed in table 4.

These estimates were made considering a time of 4.8 hours after administering the tracer. Radiation doses for the bladder, ovaries and testicles depend on the frequency of urination.

Organ	mGy/MBq	rad/mCi
Kidneys	0.0084	0.031
Bladder	0.034	0.13
Bone surface	0.061	0.23
Bone marrow	0.0093	0.034
Ovaries	0.0032	0.012
Testicles	0.0022	0.0082
Total body	0.0028	0.010

Table 4 – Dosage for administering MDP-Tc-99m

8.8. EXTERNAL RADIATION

The constant dose for technetium-99m (99m Tc) is 0.78 R/mCi*h at 1 cm. The first half-value layer is 0.017 cm of lead (Pb). Attenuation resulting from various thicknesses of lead is described in table 5.

SHIELD THICKNESS (Pb) cm	COEFFICIENT OF ATTENUATION
0.017	0.5
0.08	0.1
0.15	0.01
0.25	0.001
0.33	0.0001

Table 5 – Radiation attenuation by lead shielding.

Table 6 shows the correction for the physical decline of technetium-99m, after calibration time.

HOUR	REMAINING FRACTION	HOUR	REMAINING FRACTION
1	0,891	7	0,447
2	0,794	8	0,398
3	0,708	9	0,355
4	0,631	10	0,316
5	0,562	11	0,282
6	0,501	12	0,251

Table 6 – Physical decline; half-life of technetium-99m (99m Tc): 6.02 hours.

9. SIDE EFFECTS

Diphosphonates can cause generalized itching, dizziness, migraine, nausea and vomiting, lethargy, myalgia, arthralgia, burning sensation in the throat during the first three hours after administration. (Hesslewood, S. European system for reporting adverse reactions to and defects in radiopharmaceuticals: annual report. 2001).

10. OVERDOSE

In case of a radiation overdose with MDP-Tc-99m the patient's absorbed dose should be lowered as much as possible by ingesting more liquids to eliminate the radionuclide from the body through an increase of urination.

In case of poisoning call 0800 722 6001 for instructions of how to proceed.

RESPONSIBLE PHARMACIST
Manoela Michelon Grazziotin
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