The kit consists of reaction vials which contain the sterile, non-pyrogenic, non-radioactive ingredients necessary to produce Technetium Tc 99m Menedrate Injection for diagnostic use by intravenous injection.

Each 10 mL reaction vial contains 10.0 mg of medronic acid (as sodium salt), 1.1 mg of stannous chloride dithionate, and 2.0 mg of p-amino-terephthalic acid in lyophilized form under an atmosphere of nitrogen. Sodium hydroxide and/or hydrochloric acid has been used for pH adjustment. The addition of sterile, non-pyrogenic, and oxidant-free sodium pertechnetate Tc-99m to the vial produces a rapid labeling which is essentially quantitative and which remains stable for at least 100 hours of the preparation. The pH of the reconstituted radiopharmaceutical is 6.5 to 7.5. No bacteriostatic preservative is present.

The precise structure of the reaction vial complex or of its technetium labelled form is not known at this time.

The structural formula of medronic acid is:

\[
\text{HO} \quad \text{CH} \quad \text{OH} \\
\text{HO} \quad \text{O} \quad \text{OH} \\
\text{HO} \quad \text{O} \quad \text{OH}
\]

**ACTION**

When injected intravenously, technetium Tc-99m medronate is rapidly cleared from the blood; about 50% of the dose is accumulated and retained by the skeleton, while the remaining 50% is excreted in the urine within twenty-four hours. About 10% of the injected dose remains in the blood at one hour post-injection, 5% at 2 hours, and less than 1% remains at twenty-four hours. The resultant blood clearance curve is tri-exponential with the two faster components accounting for about 75% and the slower for about 25% of the injected dose.

Following intravenous administrations of technetium Tc-99m medronate, skeletal uptake occurs as a function of blood flow to bone and bone remodeling activity. Bone mineral crystals are generally considered to be hydroxapatite, and the complex appears to have an affinity for the hydroxapatite crystals in the bone.

The rapid blood clearance provides bone to soft-tissue ratios which favour early imaging. The skeletal uptake is bilaterally symmetrical and is greater in the axial skeleton than in long bones. Areas of abnormal osteogenesis show altered uptake making it possible to visualize a variety of osseous lesions.

**INDICATIONS AND USAGE**

Technetium Tc 99m Menedrate Injection is a skeletal imaging agent used to demonstrate areas of altered osteogenesis as seen, for example, in metastatic bone disease, Paget’s disease, arthritic disease and osteomyelitis.

**CONTRAINDICATIONS**

Hypersensitivity to this compound.

**WARNINGS**

The diphosphonate class of compounds is known to complex cations such as calcium and can create hypercalcemia as observed in animal models (see Toxicology). Therefore, caution should be exercised when administering this agent to patients who have, or who may be predisposed to hypercalcemia (i.e., alkalosis).

Preliminary reports indicate impairment of brain images using sodium pertechnetate Tc-99m injection which have been preceded by bone imaging using an agent containing stannous ions. The impairment may result in false-positive or false-negative brain images. It is recommended, where feasible, that brain imaging using sodium pertechnetate Tc-99m injection provide bone imaging procedures. Alternatively, a brain imaging agent such as technetium Tc-99m pertechnetate may be employed.

**PRECAUTIONS**

The finding of an abnormal concentration of radioactivity implies the existence of underlying pathology, but further study is required to distinguish benign from malignant lesions.

Optimal imaging results are obtained 1 to 4 hours after administration. The quality of the image may be affected by obesity, old age, and impaired renal function.

To minimize the radiation dose to the urinary bladder, the patient should be encouraged to increase his fluid intake and to void prior to the procedure.

**TOXICOLOGY**

A safety assessment using stannous medronate complex reconstituted with saline but without technetium Tc-99m or p-amino-terephthalic acid has been made in two rodent and one non-rodent species.

In mice, an intravenous injection of 100 mg/kg (2 mg/0.2 mL) did induce some clinical convulsions. No mortalities and no gross pathological changes were discovered over a 14-day observation period. A lower dose of 40 mg/kg showed no signs of intoxication and the gross necropsy was negative. Similar results were obtained in rats and beagle dogs at 20 mg/kg.

The human dose using this formulation is variable depending on the number of examinations made from the contents of one vial. In the event that this becomes a single dose of 10 mg per 70 kg or 0.15 mg/kg, these results indicate a safety factor of at least 100.

The toxicity of medronic acid has been reported to be the same as that for the ethylene-hydroxy-diphosphonate (EHDP) (intravenous LD50 40 to 55 mg/kg in mice and rabbits. Other reports showed a maximum (LD50) lethal dose of EHDP in mice to be 200 mg/kg with no deaths occurring at 100 mg/kg. The LD50 in rabbits and rats was 40 to 70 mg/kg on rapid injection of EHDP, whereas slow injection raised this to 70 to 100 mg/kg. It was demonstrated in a variety of experimental animals that acute toxic symptoms of tachycardia, hyperpnea, and tetany began at 20 to 30 mg/kg. These changes were consistent with the induction of hypocalcemia.

The role played by chelation, dilution, and speed of injection as factors in explaining the variable results of toxicity studies has been discussed in the literature.

A 14-day subacute toxicity study of stannous medronate complex was performed in mice and cats. In cats, pleuropericarditis was observed in the test groups as well as in some of the control animals. Associated renal tubular calcification was noted only in the dosed cats. Minimal local calcification was observed in the liver and heart of one mouse in the high dose group. No other significant toxicological findings were noted. The cumulative low doses in cats and in mice were 65 and 87 times greater, respectively, than the maximum probable human dose on a mg/kg basis, while the cumulative high doses were 490 and 866 times greater; respectively.

**PHYSICAL CHARACTERISTICS**

Technetium Tc-99m decay by isomeric transition with a physical half-life of 6.02 hours. The principal photon that is useful for detection and imaging studies is listed in Table 1.

---

**Table 1**

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Principal Radiation Emission Data</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Radiation</strong></td>
<td><strong>Mean %/Disintegration</strong></td>
</tr>
<tr>
<td>Gamma-2</td>
<td>85.07</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Radiation Attenuation by Lead Shielding</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Shield Thickness (Pb) cm</strong></td>
<td><strong>Coefficient of Attenuation</strong></td>
</tr>
<tr>
<td>0.017</td>
<td>0.5</td>
</tr>
<tr>
<td>0.08</td>
<td>10^-1</td>
</tr>
<tr>
<td>0.16</td>
<td>10^-2</td>
</tr>
<tr>
<td>0.25</td>
<td>10^-3</td>
</tr>
<tr>
<td>0.33</td>
<td>10^-4</td>
</tr>
</tbody>
</table>

To correct for physical decay of this radionuclide, the fractions that remain at selected intervals after the time of calibration are shown in Table 3.

**Table 3**

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Physical Decay Chart of Technetium Tc-99m</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-Life: 6.02 Hours</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Hours</strong></td>
<td><strong>Fraction Remaining</strong></td>
</tr>
<tr>
<td>0&quot;</td>
<td>1.000</td>
</tr>
<tr>
<td>0.631</td>
<td>0.562</td>
</tr>
<tr>
<td>0.631</td>
<td>0.501</td>
</tr>
<tr>
<td>0.708</td>
<td>0.398</td>
</tr>
<tr>
<td>0.794</td>
<td>0.316</td>
</tr>
<tr>
<td>1.000</td>
<td>0.251</td>
</tr>
</tbody>
</table>

---

**RADIATION DOSIMETRY**

The estimate absorbed radiation dose2 to various organs of an average patient (70 kg) from an intravenous injection of a maximum dose of 740 megabecquerels (20 mCi) of Technetium Tc 99m Menedrate Injection are shown in Table 4. The effective half-life is assumed to be the physical half-life for all calculated values.
Immediately dry the spot using a gentle stream of nitrogen gas. Do not use compressed air since this tends to cause pertech-
microlitre disposable micropipette (Fisher Scientific No. 21-164-2D) can also be used to dispense 0.02 mL.

25 gauge needle and dispense one small drop. Discard the needle and syringe after use. Instead of a tuberculin syringe a

Place a drop (approximately 0.02 mL) of the radioactive solution on a 1 cm x 10 cm chromatographic strip at a pencil mark 1 cm

Add 1 mL of the required solvent to an 18 mm x 150 mm test tube. Stopper and allow the atmosphere in the tube to equilibrate

Solvant B: Acetone for determination of pertechnetate

Solvant A: 0.9 % Sodium chloride for determination of reduced technetium

The following procedure describes a series of simple steps for running chromatograms. Step 5 describes two methods, one for

Chromatographic Methods

Radiochemical Purity

Table 4

<table>
<thead>
<tr>
<th>Organ/Tissue</th>
<th>mCi/740 MBq</th>
<th>rad/20 mCi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total body</td>
<td>1.3</td>
<td>0.13</td>
</tr>
<tr>
<td>Total bone</td>
<td>7.0</td>
<td>0.70</td>
</tr>
<tr>
<td>Red marrow</td>
<td>5.0</td>
<td>0.56</td>
</tr>
<tr>
<td>Kidneys</td>
<td>8.0</td>
<td>0.80</td>
</tr>
<tr>
<td>Liver</td>
<td>6.0</td>
<td>0.66</td>
</tr>
<tr>
<td>Bladder Wall</td>
<td>2.0</td>
<td>0.20</td>
</tr>
<tr>
<td>2.0 hr void</td>
<td>26.0</td>
<td>2.60</td>
</tr>
<tr>
<td>4.8 hr void</td>
<td>62.0</td>
<td>6.20</td>
</tr>
<tr>
<td>Orantes</td>
<td>2.4</td>
<td>0.24</td>
</tr>
<tr>
<td>2.0 hr void</td>
<td>3.4</td>
<td>0.34</td>
</tr>
<tr>
<td>Testes</td>
<td>1.6</td>
<td>0.16</td>
</tr>
<tr>
<td>4.8 hr void</td>
<td>2.2</td>
<td>0.22</td>
</tr>
</tbody>
</table>

9. The finished preparation should be discarded after 12 hours. It should also be retained during its life in a lead vial shie
d

8. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the vials contain nitrogen,

6. Assay the product in a suitable calibrator, record the radioassay information on the label with radiation warning symbol.

To prepare Technetium Tc 99m Medronate Injection:

1. Write in the space provided on the label the date and time of preparation. Apply the label to the vial shield.

2. Remove the protective disc from the reaction vial and swirl the closure with an alcohol swab.

3. Place the vial in a suitable lead vial shield which has a minimum wall thickness of 3 mm (1/8 inch) and which has a fitted lead
cap. Obtain 2 to 10 mL of sterile, non-pyrogenic sodium pertechnetate Tc-99m using a shielded syringe. The recommended

maximum amount of technetium Tc-99m (at the time of elution) to be added to a reaction vial is 18.5 gigabecquerels (500 mCi).Sufficient sodium pertechnetate is to be used for the reconstitution of a reaction vial to ensure that the dose of

medronate administered does not exceed 10 mg. Sodium pertechnetate Tc-99m solutions containing an oxidizing agent are

not suitable for use.

Using a shielded syringe, aseptically add the sodium pertechnetate Tc-99m solution to the reaction vial, while avoiding the

build-up of excessive pressure in the vial. Pressure build up may be avoided by injecting several millilitres of pertechnetate

solution into the reaction vial, then withdrawing several millilitres of nitrogen gas (to prevent oxidation of the compo-

sites) into the syringe. The procedure is repeated as necessary until the entire amount of pertechnetate is added to the vial and

normal pressure is established within the vial.

5. Place the lead cap on the vial shield and agitate the shielded vial until the contents are completely dissolved. To ensure

maximum radio labelling, allow the preparation to stand for 5 to 15 minutes at room temperature (15 °C to 30 °C) after

mixing. Using proper shielding, the reaction vial should be visually inspected to ensure that the solution is clear and free of

particulate matter before proceeding; if it is not, the radiopharmaceutical should not be used.

6. Assembly the product in a suitable calibrator, record the radioassay information on the label with radiation warning symbol.

7. The radiochemical purity of the finished preparation should be determined prior to patient administration. The radiochem-

ical purity should not be less than 90 %.

8. Withdrawals for administration must be made aseptically using a sterile needle and syringe. Since the vials contain nitrogen,

the vials should not be vented. If repeated withdrawals are made, the replacement of the contents from the vial with air

should be minimized.

9. The finished preparation should be discarded after 12 hours. It should also be retained during its life in a lead vial shield

with the lead cap in place.

Radiochemical Purity

Chromatographic Methods

The following procedure describes a series of simple steps for running chromatograms. Step 5 describes two methods, one for
determining free pertechnetate in a mixture of chelated and reduced technetium and the other for determining reduced techn-
etium in a mixture of chelated technetium and pertechnetate. The TLC procedure requires the following:

For the preparation of Technetium Tc 99m Medronate Injection

Part I

Part II

Part III

Part IV

The unreconstituted reaction vials may be stored at or below room temperature (2 °C – 30 °C). After labelling with technetium
Tc-99m, the radiopharmaceutical may also be stored at or below room temperature (2 °C – 30 °C).

EXPiry

The finished preparation should be discarded 12 hours after reconstitution. Do not use the kit beyond the expiry date stamped on
the box.

REFERENCES


for selected radiopharmaceuticals and organs, ADRD Pamphlet No. 11, 1975.

Renewed: January 2011

Imported by:  
Jubilant Drachman Limited  
A-38, 2nd Floor, Globus Bagh,  
Opp. Metro Pillar No. 738,  
Main Nagpaham Road,  
New Delhi – 110039

Jubilant Drachman Ltd.  
Kirkland, Quebec, Canada

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In the acetone system, the bound and reduced fractions stay at the origin while free pertechnetate 99mTcO4– migrates to the
front Rf 0.85 to 1.0.

Step 5

Method A – Determination of reduced technetium, using saline solvent:

Cut the dried strip 3 cm from the origin end. The short piece is marked as Part I and the long piece is marked as Part II. Count
the pieces in a suitable counter and determine the percentage of reduced technetium according to the following formula:

Percent 99mTcO2+ = Counts in Part I / Counts in Part II X 100

Method B – Determination of pertechnetate using acetone:

Cut the dried strip 2 cm from the solvent front end. The short piece is marked Part II and the long piece is marked Part III. Count
the pieces in a suitable counter and determine the percentage of free pertechnetate according to the following formula:

Percent 99mTcO4– = Counts in Part II / Counts in Part III X 100

NOTE: IT IS IMPORTANT TO NOTE THAT THE STRIPS ARE CUT IN DIFFERENT POSITIONS FOR METHODS A AND B.

Step 6

Determine the amount of bound technetium according to the following formula:

Percent chelated 99mTc = 100 – % 99mTcO4–

Step 7

Store all waste radioactive strips for 48 hours before disposing of them as non-radioactive waste. Store used chromatographic
solvents in a similar fashion.

STORAGE

The unreacted reaction vials may be stored at or below room temperature (2 °C – 30 °C). After labelling with technetium
Tc-99m, the radiopharmaceutical may also be stored at or below room temperature (2 °C – 30 °C).

Table 4 Estimated Absorbed Radiation Doses

In the saline system, reduced 99mTcO2+ stays at the origin (Rf 0), while the bound and free technetium 99mTcO4– move to the
front Rf 0.85 to 1.0.