



World Health
Organization

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3 **Monograph for Technetium (^{99m}Tc) medronate complex injection**
4 **(Technetii (^{99m}Tc) medronati multiplex injectio)**
5 **(September 2017)**

6
7 ***DRAFT FOR COMMENT***
8

Please send any comments on the revision of this draft document to Dr Sabine Kopp Group Lead, Medicines Quality Assurance, Technologies Standards and Norms (kopps@who.int) with a copy to Ms Xenia Finnerty (finnertyk@who.int) by 1 November 2017.

Our working documents will be sent out electronically only and will also be placed on the Medicines website for comment under “Current projects”. If you do not already receive our draft working documents please let us have your email address (to bonnyvw@who.int) and we will add it to our electronic mailing list.

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36 **SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.731**

37 Monograph for Technetium (^{99m}Tc) medronate complex injection

38 (Technetii (^{99m}Tc) medronati multiplex injectio)

39

40

	Date
IAEA consultation	3–7 December 2012
IAEA consultation	6–10 May 2013
Draft monograph received from IAEA in track-change mode according to format/template described in QAS/13.544	June 2013
Discussion at informal consultation on new medicines, quality control and laboratory standards	12–14 June 2013
Feedback to IAEA by WHO Secretariat	June 2013
Circulation for comments to IAEA and WHO Panel of Experts	June 2013
Feedback to IAEA, as appropriate	August–September 2013
Discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations	October 2013
Follow up by IAEA, including review of comments received	October 2013–February 2014
Discussion of revised version at IAEA consultation, Vienna, Austria	February 2014
Finalization by IAEA	February 2014
Circulation of revision to WHO and IAEA mailing list of experts for comments	March 2014
Compilation of feedback	April 2014
Discussion at informal consultation on Specifications for The International Pharmacopoeia and laboratory standards in Geneva	3–4 April 2014

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Compilation of feedback to IAEA	May 2014
Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations	13–17 October 2014
Update during the fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations	12–16 October 2015
Review and discussion of situation regarding monograph development for radiopharmaceuticals at informal consultation on quality control laboratory tools and specifications for medicines	9–11 May 2016
IAEA update during the fifty-first WHO Expert Committee on Specifications for Pharmaceutical Preparations	17–21 October 2016
Review and discussion during informal consultation on quality control laboratory tools and specifications for medicines	2–4 May 2017
IAEA delegated final review and modifications to Professor Alain Nicolas, France	May–September 2017
Mailing of revised monograph for public consultation	September 2017
Presentation to the fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations	16–20 October 2017
Any further action as necessary	

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47 **Monograph for Technetium (^{99m}Tc) medronate complex injection**

48 **(Technetii (^{99m}Tc) medronati multiplex injectio)**

49

50 **Latin.** Technetii (99mTc) medronati multiplex injectio

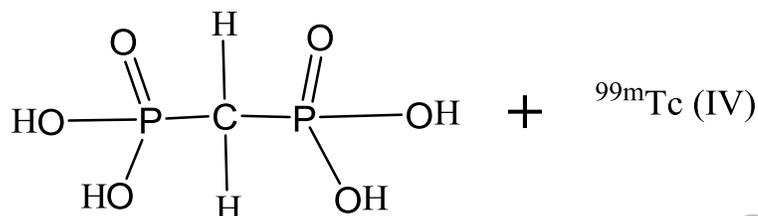
51

52 **English.** Technetium (99mTc) medronate complex injection

53

54 **Structural formula**

55



Medronoic acid:(MDP: CH₆O₆P₂)

57

Chemical name: Methylenebis(phosphonic acid)

58

59 **Other names.** (^{99m}Tc)-Methylene diphosphonate complex injection, (^{99m}Tc)-MDP injection.

60

61 **Description.** Technetium (^{99m}Tc) medronate complex injection is a clear, colourless aqueous
62 solution.

63

64 Technetium-99m has a half-life of 6.02 hours.

65

66 **Category.** Diagnostic.

67

68 **Storage.** Technetium (^{99m}Tc) medronate complex injection should be kept at a temperature
69 between 2 °C to 8 °C.

70

71 **Labelling.** The label complies with the General monograph [Radiopharmaceuticals](#).

72

73 **Manufacture**

74

75 Technetium (^{99m}Tc) medronate complex injection is prepared aseptically from sterile starting
76 materials such as a sterile kit containing sodium methylene diphosphonate and stannous salt with
77 [Sodium pertechnetate \(^{99m}Tc\) injection \(Fission\)](#) or [Sodium Pertechnetate \(^{99m}Tc\) injection](#)
78 [\(Non-fission\)](#). It may have the pH adjusted and may contain reducing, chelating, stabilizing,
79 filling and antioxidizing agents as well as antimicrobial preservatives and buffers. The injection
80 may also be prepared under aseptic processing combined with sterilization by filtration (see [5.8](#)
81 [Methods of sterilization](#)).

82

83 **Additional information**

84
85 Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in
86 millilitres.

87
88 **Requirements**

89
90 Complies with the monograph for [Parenteral Preparations](#) and with that for
91 [Radiopharmaceuticals](#).

92
93 **Definition**

94
95 Technetium (^{99m}Tc) medronate complex injection is a sterile solution of sodium methylene
96 diphosphonate (sodium medronate) that is complexes with technetium-99m, in presence of a
97 stannous salt or other suitable reducing agent. The injection is suitable for intravenous
98 administration and contains sufficient sodium chloride to make the solution isotonic. The content
99 of technetium-99m is not less than 90% and not more than 110% stated on the label at the
100 reference date and time. Not less than 95% of the total technetium-99m radioactivity is present as
101 technetium (^{99m}Tc) medronate complex. The injection contains a variable quantity of tin (Sn) not
102 greater than 3 mg/mL [*Note from the Secretariat: suggestion to amend to 3 mg/V*].

103
104 **Identity tests**

- 105
106 • Either tests A, C and D or tests B, C and D may be applied
- 107
108 A. Record the gamma-ray spectrum using a suitable instrument with a sample of technetium-
109 99m, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of
110 a specimen of technetium-99m in that it exhibits a major peak of 141 keV.
- 111
112 Standardized technetium-99m solutions are available from laboratories recognized by the
113 relevant national or regional authority.
- 114
115 B. The half-life determined using a suitable detector system is between 5.72 and 6.32 hours.
- 116
117 C. Examine the radiochromatograms obtained in the test for Radiochemical purity. The
118 retardation factor of the principal peak in the radiochromatogram obtained with the test
119 solution in test 1 (system A) is 0.0 and in (system B) is 1.0.
- 120
121 D. Thin-layer chromatography. The injection may be released for use before completion of the
122 test.

123
124 *Test solution.* Dilute the preparation to be examined with [water R](#) to obtain a solution
125 containing about 0.1 mg/mL of medronic acid.

126
127 *Reference solution (a).* Dissolve 3 mg of [sodium oxidronate R](#) in [water R](#) and dilute to
128 10 mL with the same solvent.

129 *Reference solution (b).* Dissolve 1 mg of [medronic acid R](#) in [water R](#) and dilute to 10 mL
130 with the same solvent.

131
132 *Plate:* [cellulose for chromatography R](#) as the coating substance.

133
134 *Mobile phase:* to 30 mL of [water R](#) add 35 mL of [ethanol \(96 per cent\) R](#), 15 mL of [2-](#)
135 [methylpropanol R](#), 0.4 mL of [concentrated ammonia R](#), 5 g of [trichloroacetic acid R](#) and
136 20 mL of [2-propanol R](#) and mix.

137
138 *Application:* about 5 µL, applied in 1 µL portions with drying after each application.

139
140 *Development:* over 2/3 of the plate.

141
142 *Drying:* in air for at least 14 hours.

143
144 *Detection:* spray with a solution prepared as follows: to 25 mL of a 40 g/L solution
145 of [ammonium molybdate R](#) add 63 mL of [water R](#), 2 mL of [hydrochloric acid R](#), 2 mL
146 of [sulfuric acid R](#) and 8 mL of [perchloric acid R](#) and mix. Expose the plate to ultraviolet
147 light at 254 nm for 15 minutes.

148
149 *System suitability:* the retardation factor of the spot in the chromatogram obtained with
150 reference solution (b) is about 0.6 and clearly different from that obtained with reference
151 solution (a), which is about 0.5.

152
153 *Results:* the principal spot in the chromatogram obtained with the test solution is similar in
154 position and colour to the principal spot in the chromatogram obtained with reference
155 solution (b).

156
157 **pH.** Carry out the test as described under [1.13 or R1.5 Determination of pH](#) under the
158 monograph for [Radiopharmaceuticals](#), the pH value of the injection, should be between 3.5 and
159 7.5.

160
161 **Tin.** Determine the content of tin using a [semi-quantitative tin test kit R](#), following the
162 instructions given by the test kit manufacturer. If necessary, dilute the preparation to be
163 examined with [water R](#) to obtain a concentration of tin within the measurement range of the test
164 kit.

165
166 Not more than 3 mg of Sn per mL [*Note from the Secretariat: suggestion to amend to 3 mg/V*].

167
168 **Sterility.** Test for sterility will be initiated on the day of manufacture. The injection may be
169 released for use before completion of the test.

170
171 The injection complies with [3.2 Test for sterility](#), modified as described in the monograph for
172 [Radiopharmaceuticals](#).

173
174 **Bacterial endotoxins.** The test must be completed before release of the preparation for use.

175
176 Perform the test as described under [3.4 Test for bacterial endotoxins](#), modified as described in
177 the monograph for [Radiopharmaceuticals](#). The injection contains not more than 175/V I.U. of
178 endotoxins per mL.

179
180 **Radiochemical purity**

181
182 Perform the test as described under [1.14.1 Thin-layer chromatography](#) using two separate
183 systems: system (A) and system (B). Silica gel R to be used as the coating substance and methyl
184 ethyl ketone R (system A) or sodium acetate (1 mol/L) VS (system B) as the mobile phase.
185 Apply to the plates about 5 µL of the injection to be examined, suitably diluted to give an
186 optimum count rate and develop for a distance of about 10 cm. Allow the plates to dry and
187 determine the radioactivity distribution by a suitable method.

188
189 In system (A) the technetium (^{99m}Tc) medronate complex and reduced hydrolysed technetium-
190 99m have a Rf value of 0.0–0.1 and the pertechnetate ion has a Rf value of 0.9–1.0.

191
192 In system (B) the technetium (^{99m}Tc) medronate complex and the pertechnetate ion have an Rf
193 value of 0.9–1.0 and reduced hydrolysed technetium-99m has an Rf value of 0.0–0.1.

194
195 The sum of the percentages of radioactivity corresponding to the pertechnetate ion (Impurity B)
196 in system (A) and reduced hydrolysed technetium-99m (Impurity A) in system (B) is less than
197 5% of the total radioactivity due to technetium-99m. Not less than 95% of the total technetium-
198 99m radioactivity is present as technetium (^{99m}Tc) medronate complex.

199
200 **Radioactivity**

201
202 Measure the radioactivity using a suitable counting instrument as described under [R.1.1](#)
203 [Detection and measurement of radioactivity](#).

204
205 **Impurities**

- 206
207 A. [^{99m}Tc]technetium in colloidal form
208 B. [^{99m}Tc]pertechnetate ion.

209
210 ***