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3 **Monograph for Technetium (^{99m}Tc) sestamibi complex injection**

4 **(Technetii (^{99m}Tc) sestamibi multiplex injection)**

5 **(September 2017)**

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DRAFT FOR COMMENT

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 bonnyw@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/17.737**37 Monograph for Technetium (^{99m}Tc) sestamibi complex injection38 (Technetii (^{99m}Tc) sestamibi multiplex injection)

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	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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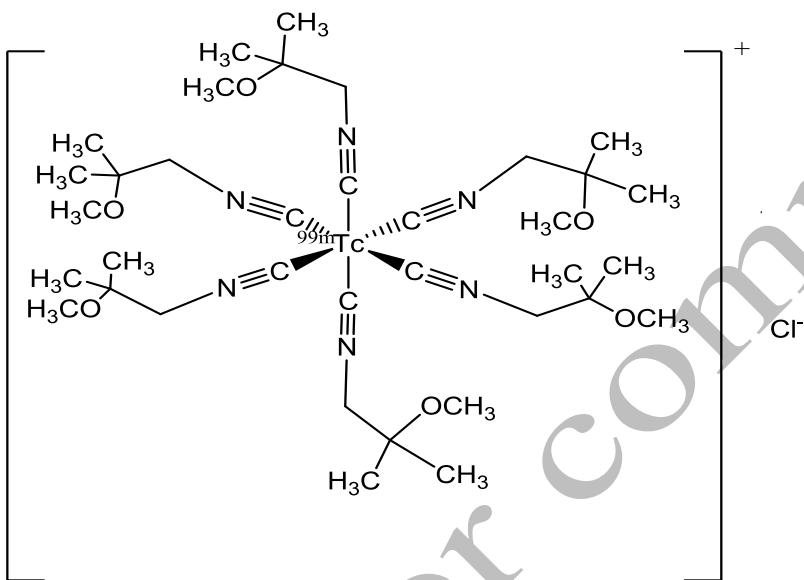
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Monograph for Technetium (^{99m}Tc) sestamibi complex injection (Technetii (^{99m}Tc) sestamibi multiplex injection)

Latin. [^{99m}Tc]Technetii sestamibi multiplex injectio.

English. $[^{99m}\text{Tc}]$ Technetium sestamibi complex injection.

Structural formula



Molecular formula. $C_{36}H_{66}N_6O_6^{99m}Tc$

Relative molecular mass. 777.85

Chemical name. (OC-6-11)-hexakis [1-(isocyano- κ C)-2-methoxy-2-methylpropane] 99m Tc-technetium(I) chloride

Other name. $[^{99m}\text{Tc}]$ -MIBI injection

Description. $[^{99m}\text{Tc}]$ Technetium sestamibi complex injection is a clear, colourless aqueous solution.

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

Category. Diagnostic.

Storage. $[^{99m}\text{Tc}]$ Technetium sestamibi complex injection is stored at room temperature with adequate shielding.

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

77

78 **Manufacture**

79

80 $[^{99m}\text{Tc}]$ Technetium sestamibi complex injection may be prepared aseptically by heating a
81 mixture containing [tetrakis(2-methoxy-2-methylpropyl-1-isocyanide) copper(1+)]
82 tetrafluoroborate, a weak chelating agent and a stannous salt with [Sodium pertechnetate \(\$^{99m}\text{Tc}\$ \)](#)
83 [injection \(Fission\)](#) or [Sodium Pertechnetate \(\$^{99m}\text{Tc}\$ \) injection \(Non-fission\)](#), the mixture in
84 boiling water for 10 minutes to allow the complex formation, then cooled to room temperature
85 for 15 minutes. The injection may have the pH adjusted and may contain reducing, stabilizing,
86 filling and antioxidantizing agents as well as antimicrobial preservatives and buffers. The injection
87 may also be prepared under aseptic processing combined with sterilization by filtration (see [5.8](#)
88 [Methods of sterilization](#)). $[^{99m}\text{Tc}]$ Technetium MIBI injection should be used within 4 hours from
89 the stated date and hour of the preparation.

90

91

92 **Additional information**

93

94 Wherever V is used within the tests of this monograph, V is the maximum recommended dose in
95 millilitres.

96

97 **Requirements**

98

99 Complies with the monograph for [Parenteral Preparations](#) and with that for
100 [Radiopharmaceuticals](#).

101

102 **Definition**

103

104 Technetium (^{99m}Tc) MIBI injection is a sterile solution of (*OC*-6-11)-hexakis[1-(isocyano- κ C)-2-
105 methoxy-2-methylpropane] $[^{99m}\text{Tc}]$ technetium(I) chloride, a stannous salt and [Sodium](#)
106 [pertechnetate \(\$^{99m}\text{Tc}\$ \) injection \(Fission\)](#) or [Sodium Pertechnetate \(\$^{99m}\text{Tc}\$ \) injection \(Non-fission\)](#).
107 The injection is suitable for intravenous administration and contains sufficient sodium chloride to
108 make the solution isotonic. The content of technetium-99m is not less than 90% and not more
109 than 110% of the content of technetium-99m stated on the label at the reference date and time
110 stated on the label. Not less than 90% of the total technetium-99m radioactivity is present as
111 $[^{99m}\text{Tc}]$ technetium sestamibi complex.

112

113 **Identity tests**

114

115 • Either tests A and C or tests B and C may be applied.

116

117 A. Record the gamma-ray spectrum using a suitable instrument with a sample of technetium-
118 99m, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of
119 a specimen of technetium-99m in that it exhibits a major peak of 141 keV.

120

121 Standardized technetium-99m solutions are available from laboratories recognized by the
122 relevant national or regional authority.

123 B. The half-life determined using a suitable detector system is between 5.72 and 6.32 hours.

124 C. In the test for Radiochemical purity, the chromatogram obtained contributes to the
125 identification of the [^{99m}Tc]Technetium MIBI.

126 **pH.** Perform the test as described under [R1.5 or 1.13 Determination of pH](#) under the monograph
127 for [Radiopharmaceuticals](#), the pH of the injection should be between 5.0 and 6.0.

128 **Sterility.** Test for sterility will be initiated on the day of manufacture. The injection may be
129 released for use before completion of the test. The injection complies with [3.2 Test for sterility](#),
130 modified as described in the monograph for [Radiopharmaceuticals](#).

131 **Bacterial endotoxins.** The test must be completed prior to the preparation release.

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

135 **Radiochemical purity.** Test 1 and test 2 to be performed.

136 **Test 1. Impurity A and other polar impurities.** Perform the test as described under [1.14.1](#)
137 [Thin-layer chromatography](#), using (10 mm × 75 mm) TLC octadecylsilyl silica gel plate R as the
138 coating substance. The mobile phase is prepared by mixing 10 volumes of tetrahydrofuran R, 20
139 volumes of a 38.5 g/L solution of ammonium acetate R, 30 volumes of methanol R and 40
140 volumes of acetonitrile R. Apply to the plate about 5 µL of the injection to be examined. The
141 plate is placed in a chromatographic chamber and the chromatogram is developed in a freshly
142 prepared (not more than 4 hours) mobile phase until the solvent front has moved about 6 cm
143 from the origin. Allow the plate to dry in air and determine the radioactivity distribution by a
144 suitable radioactivity detector.

145 In this system, the [^{99m}Tc]technetium MIBI and impurity C are located at Rf value of about 0.3 to
146 0.6, impurity A (free pertechnetate) and other polar impurities are located at Rf value of about
147 0.9 to 1.0, and impurity B (the radiolabelled colloid) is located at Rf value of about 0.0 to 0.1.

148 **Test 2.** Perform the test as described under [1.14.4 High-performance liquid chromatography](#)
149 using a stainless steel column (l = 0.25 m, Ø = 4.6 mm). The stationary phase is spherical base-
150 deactivated, end-capped octadecylsilyl silica gel for chromatography R (5 µm). The mobile
151 phase is prepared by mixing 20 volumes of acetonitrile R, 35 volumes of a 6.6 g/L solution of
152 ammonium sulfate R and 45 volumes of methanol R. The flow rate is 1.5 mL/min, the detector is
153 radioactivity detector. Inject 25 µL of the injection under test, record the chromatograms, and
154 measure the area percentage for all of the peaks present. The retention time for ^{99m}Tc-MIBI is
155 about 12 to 14 minutes. The relative retention of impurity C with reference to technetium-99m

166 sestamibi is about 1.3–1.5. Correct for the presence of colloid, that is not measured by this
 167 method through the following equation:

168

$$C_f = \frac{100 \% - A_c}{100}$$

169

170

171 where C_f is the correction factor, and A_c is the mean area percentage for the colloid obtained
 172 from Method 1. The corrected area percentage is obtained by multiplying the correction factor
 173 (C_f) to the area percentage of the peaks present in the chromatogram.

174

175 Not less than 90% (corrected area percentage) of the total radioactivity is present as ^{99m}Tc -MIBI.

176 Not more than 5% (corrected area percentage) of total radioactivity is present as impurity C.

177

178 **Radioactivity**

179

180 Measure the radioactivity using suitable calibrated counting instrument as described under [R.1.1](#)
 181 *Detection and measurement of radioactivity*.

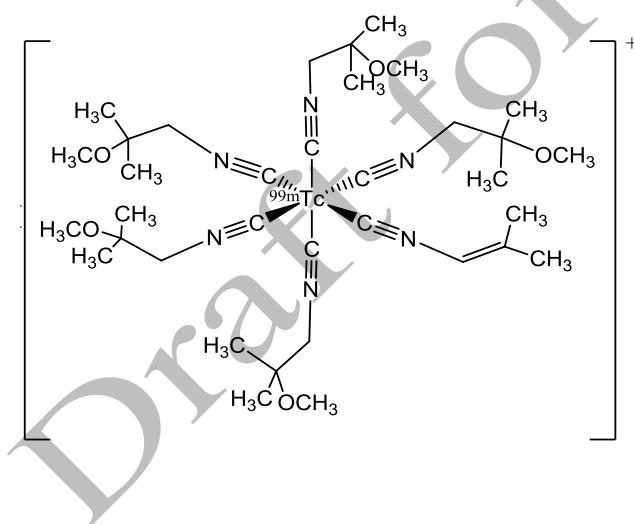
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183 **Impurities**

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- 185 A. $^{99m}\text{Tc}]\text{O}_4^-$: (^{99m}Tc)pertechnetate ion,
- 186 B. technetium-99m in colloidal form,
- 187 C. (*OC*-6-22)-pentakis[1-(isocyano- κ C)-2-methoxy-2-methylpropane][1-(isocyano- κ C)-2-
 188 methylprop-1-ene] $^{[99m}\text{Tc}]$ technetium (1+).

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