World Health Organization

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

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

(September 2017)

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.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.737

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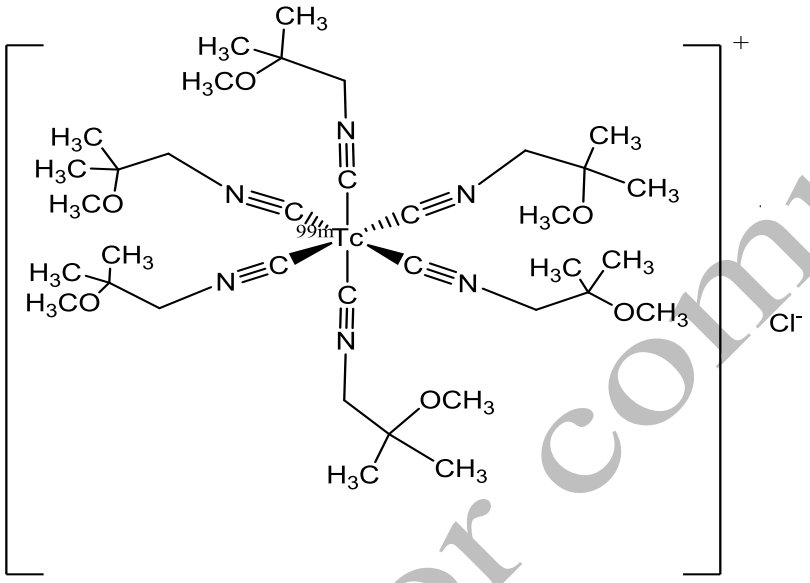
(Technetii (^{99m}Tc) sestamibi multiplex injection)

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

English. [^{99m}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}Tc]-MIBI injection

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

Labelling. The label complies with the General monograph *Radiopharmaceuticals*.

Manufacture

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

Additional information

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

Requirements

Complies with the monograph for *Parenteral Preparations* and with that for *Radiopharmaceuticals*.

Definition

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

Identity tests

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

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

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

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

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

pH. Perform the test as described under *R1.5 or 1.13 Determination of pH* under the monograph for *Radiopharmaceuticals*, the pH of the injection should be between 5.0 and 6.0.

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

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

Perform the test as described under *3.4 Test for bacterial endotoxins*, modified as described in the monograph for *Radiopharmaceuticals*. The injection contains not more than 175/V I.U. of endotoxins per millilitre.

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

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

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

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

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

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

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

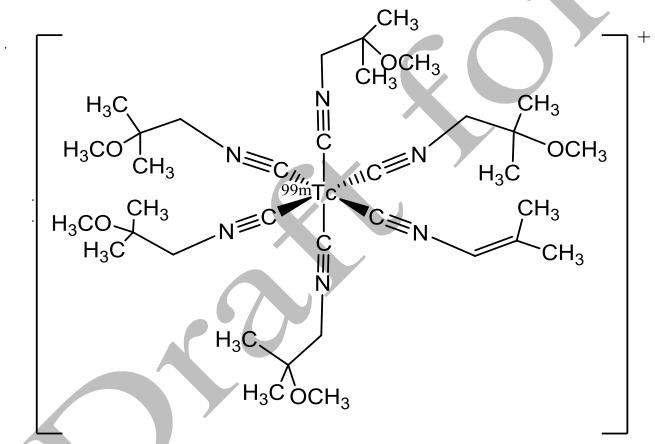
Not less than 90% (corrected area percentage) of the total radioactivity is present as ^{99m}Tc-MIBI. Not more than 5% (corrected area percentage) of total radioactivity is present as impurity C.

Radioactivity

Measure the radioactivity using suitable calibrated counting instrument as described under *R.1.1 Detection and measurement of radioactivity*.

Impurities

A. [^{99m}Tc]O_4^-: (^{99m}Tc)pertechnetate ion,
B. technetium-99m in colloidal form,
C. (*OC*-6-22)-pentakis[1-(isocyano-κ*C*)-2-methoxy-2-methylpropane][1-(isocyano-κ*C*)-2-methylprop-1-ene][^{99m}Tc]technetium (1+).



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