Monograph for Technetium (99mTc) bicisate complex injection
(99mTc) bicisati multiplex injectio
(September 2017)

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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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.736

**Monograph for Technetium (\(^{99m}\text{Tc}\)) bicisate complex injection**

(\(\text{Technetii (}^{99m}\text{Tc}\) bicisati multiplex injectio)

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<tr>
<td>IAEA consultation</td>
<td>3–7 December 2012</td>
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<tr>
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<td>6–10 May 2013</td>
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<tr>
<td>Draft monograph received from IAEA in track-change mode according to format/template described in QAS/13.544</td>
<td>June 2013</td>
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<tr>
<td>Discussion at informal consultation on new medicines, quality control and laboratory standards</td>
<td>12–14 June 2013</td>
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<td>Feedback to IAEA by WHO Secretariat</td>
<td>June 2013</td>
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<td>Circulation for comments to IAEA and WHO Panel of Experts</td>
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<td>Feedback to IAEA, as appropriate</td>
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<td>Discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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<td>Follow up by IAEA, including review of comments received</td>
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<td>Circulation of revision to WHO and IAEA mailing list of experts for comments</td>
<td>March 2014</td>
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<td>Compilation of feedback</td>
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<tr>
<td>Discussion at informal consultation on Specifications for The International Pharmacopoeia and laboratory standards in Geneva</td>
<td>3–4 April 2014</td>
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<td>Event</td>
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<tr>
<td>Compilation of feedback to IAEA</td>
<td>May 2014</td>
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<tr>
<td>Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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<td>Update during the fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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<td>Review and discussion of situation regarding monograph development for radiopharmaceuticals at informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>9–11 May 2016</td>
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<td>IAEA update during the fifty-first WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>17–21 October 2016</td>
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<td>Review and discussion during informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>2–4 May 2017</td>
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<tr>
<td>IAEA delegated final review and modifications to Professor Alain Nicolas, France</td>
<td>May–September 2017</td>
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<tr>
<td>Mailing of revised monograph for public consultation</td>
<td>September 2017</td>
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<td>Presentation to the fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>16–20 October 2017</td>
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<tr>
<td>Any further action as necessary</td>
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Monograph for Technetium $^{99m}$Tc bicisate complex injection

*(Technetii $^{99m}$Tc bicisati multiplex injection)*

**Note from the Secretariat:** Justify the use of 3 different systems to establish radiochemical purity, e.g. the use of only Test 1 System A to comply with the specifications for technetium $^{99m}$Tc bicisate complex and sum of the impurities.

Check the specifications for the pH.

**Latin.** Technetii $^{99m}$Tc bicisati multiplex injection

**English.** Technetium $^{99m}$Tc bicisate complex injection

**Structural formula**

![Structural formula](image)

**Molecular formula.** $C_{12}H_{21}N_2O_5S_2^{99m}$Tc

**Relative molecular mass.** 436.34

**Chemical name**

$(2R)$-3-ethoxy-2-[(2R)-1-ethoxy-1-oxo-3-sulfidopropan-2-yl]azanidylethylamino]-3-oxopropane-1-thiolate oxotechnetium-99m.

**Other names.** $^{99m}$Tc-Ethylene dicysteine diester complex injection, $^{99m}$Tc-Ethyl cysteinate dimer, $^{99m}$Tc-ECD injection, Neurolite, $^{99m}$Tc-L,L-ECD, $[N,N$-ethylenedi-L-cysteinato(3-)]$^{99m}$Tc$|$technetium(V) diethyl ester.

**Description.** Technetium $^{99m}$Tc bicisate complex injection is a clear, colourless aqueous solution.

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

**Category.** Diagnostic.

**Storage.** Technetium $^{99m}$Tc bicisate complex injection should be kept at room temperature between 15 °C to 25 °C with adequate shielding.

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

Technetium ($^{99m}$Tc) bisicate complex injection is prepared from $N,N'$-(1,2-ethylenediyl)bis[(2R)-2-amino-3-sulfanylpropanoic acid] diethyl ester and stannous salt with Sodium pertechnetate ($^{99m}$Tc) injection (Fission) or Sodium Pertechnetate ($^{99m}$Tc) injection (Non-fission). It may have the pH adjusted and may contain reducing, chelating, 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).

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) bisicate complex injection is a sterile solution of bisicate dihydrochloride complexed with technetium-99m. 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. Not less than 90% of the total technetium-99m radioactivity is present as ($^{99m}$Tc) bisicate 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 141keV.

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 technetium ($^{99m}$Tc) bisicate complex.

pH. Carry out the test as described under 1.13 or R1.5 Determination of pH under the monograph for Radiopharmaceuticals, the pH of the injection should be between 6.0 and 8.0 [Note from the Secretariat: suggestion to amend to 6.5 to 7.5].
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. Solutions should be freshly prepared. The injection to be examined should be incubated at room temperature for at least 30 minutes after preparation.

Either test 1 or 2 may be applied

**Test 1.** Systems A and B to be performed.

**System A.** Radiochemical purity of technetium (99mTc) bicisate complex.

Perform the test of radiochemical purity as described under 1.14.1 Thin-layer chromatography. Prepare four vials of injections and perform the test on each vial. Apply 5 µL of injection 2 cm from the bottom of a 2.5 cm x 7.5 cm thin-layer chromatographic (TLC) silica gel sheet. Allow the spot to dry for 5 to 10 minutes. Place the plate in a pre-equilibrated TLC tank containing HPLC grade ethyl acetate, and develop the chromatogram until 4/5 of the plate is reached. Remove the plate and allow it to dry in a current of air. Cut the chromatographic sheet 4.5 cm from the bottom. Count the activity in each piece using suitable detector. The activity of the upper portion contains the technetium (99mTc) bicisate complex and the activity in the lower section contains all radioimpurities. Calculate the percentage of radiochemical purity of technetium (99mTc) bicisate complex by the following formula:

\[
\text{99mTc- bicisate (\%) = 100 U / (U + L)}
\]

where:

U = activity of the upper piece of plate, L = activity of the lower piece of the plate.

Not less than 90% of the total technetium-99m radioactivity is found as technetium (99mTc) bicisate complex. The sum of the percentages of radioactivity corresponding to the impurities is not more than 10%. Calculate the mean percent radiochemical purity for the four vials.

**System B.** Determination of related radiochemical impurities.

(This test is performed on the same test specimen used to perform the Radiochemical purity test. Perform the tests in parallel with a minimal delay in spotting of the chromatographic media following the 30-minute incubation period.)
Perform the test as described under **1.14.1 Thin-layer chromatography**. Apply about 2 µL of the injection 1 cm from the bottom of a 2.5 cm x 7.5 cm reverse-phase thin-layer chromatographic plate and allow the spot to air-dry. Place the plate into a developing tank containing a mixture of acetone R and ammonium acetate 0.5 M (60:40 V/V) as the mobile phase. Develop the plate until the 7 cm line is reached. Remove the plate and allow it to dry in a current of air. Determine the distribution of activity using suitable calibrated counting instrument. Determine the compounds present by calculating the retention factors for all peaks present. Compounds and approximate R<sub>f</sub> values are as follows:

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Approximate R&lt;sub&gt;f&lt;/sub&gt; values</th>
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</thead>
<tbody>
<tr>
<td>((^{99m})Tc) bicisate</td>
<td>0.15–0.44</td>
</tr>
<tr>
<td>(^{99m})Tc (IV) bicisate</td>
<td>0.3–0.4</td>
</tr>
<tr>
<td>Technetium ((^{99m})Tc) bicisate and (^{99m})Tc (IV) bicisate</td>
<td>0.15–0.44</td>
</tr>
<tr>
<td>Hydrolysed reduced Tc</td>
<td>0.00–0.14</td>
</tr>
<tr>
<td>Free pertechnetate and (^{99m})Tc ethylene cisteinate monomer</td>
<td>0.70–0.84</td>
</tr>
<tr>
<td>(^{99m})Tc EDTA</td>
<td>0.95–1.0</td>
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</tbody>
</table>

Calculate the quantity of technetium (\(^{99m}\)Tc) (IV) bicisate complex by subtracting the percentage of technetium (\(^{99m}\)Tc) bicisate complex obtained in the system A from combined technetium (\(^{99m}\)Tc) bicisate complex and technetium (\(^{99m}\)Tc) (IV) bicisate complex obtained in system B. The sum of the impurities is not more than 10% of the total radioactivity.

**Test 2.** Perform the test as described under **1.14.2 Paper chromatography** and ascending conditions using paper for chromatography R Whatman No 1 (3 cm x 23 cm). The solvent to be used is methanol (100%). Spot about 2–5 µL of \(^{99m}\)Tc bicisate complex injection at the point of spotting marked at 3 cm from one end of the paper in duplicate. Develop the chromatogram, over 60 minutes, till the solvent front reaches 15 cm from the point of spotting. Allow the strip to dry and determine the radioactivity distribution by scanning with a suitable radiation detector.

The R<sub>f</sub> values of \(^{99m}\)Tc-bicisate complex, \(^{99m}\)Tc-pertechnetate and \(^{99m}\)Tc-reduced, hydrolyzed technetium are 0.5–1.0, 0.2–0.4 and 0.0–0.1, respectively.

Calculate the % of activity present as \(^{99m}\)Tc-bicisate complex as follows:

\[
\text{(% RCP (Radiochemical purity))} = \frac{\text{Activity in the } ^{99m}\text{Tc–bicisate complex zone}}{\text{Total Activity}} \times 100
\]

The radiochemical purity shall be not less than 90%.

In this system, all the impurities remain below Rf 0.4.
Radioactivity

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

Impurities

A. Technetium-99m in colloidal form,

B. $[^{99m}\text{Tc}]$ pertechnetate ion,

C. Complex of technetium-99m with ethyl hydrogen N,N'-ethylenedi-L-cysteinate,

D. Complex of technetium-99m with N,N'-ethylenedi-L-cysteine,

E. Complex of technetium-99m with mannitol,

F. Complex of technetium-99m with disodium edetate.