Monograph for Sodium pertechnetate ($^{99m}\text{Tc}$) injection (fission)  
(Natrii pertechnetatis ($^{99m}\text{Tc}$) fissione formati injectio)  
(Sepetember 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.

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Please send any request for permission to:

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<table>
<thead>
<tr>
<th>Event</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAEA consultation</td>
<td>3–7 December 2012</td>
</tr>
<tr>
<td>IAEA consultation</td>
<td>6–10 May 2013</td>
</tr>
<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>
</tr>
<tr>
<td>Discussion at informal consultation on new medicines, quality control and laboratory standards</td>
<td>12–14 June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA by WHO Secretariat</td>
<td>June 2013</td>
</tr>
<tr>
<td>Circulation for comments to IAEA and WHO Panel of Experts</td>
<td>June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA, as appropriate</td>
<td>August–September 2013</td>
</tr>
<tr>
<td>Discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>October 2013</td>
</tr>
<tr>
<td>Follow up by IAEA, including review of comments received</td>
<td>October 2013–February 2014</td>
</tr>
<tr>
<td>Discussion of revised version at IAEA consultation, Vienna, Austria</td>
<td>February 2014</td>
</tr>
<tr>
<td>Finalization by IAEA</td>
<td>February 2014</td>
</tr>
<tr>
<td>Circulation of revision to WHO and IAEA mailing list of experts for comments</td>
<td>March 2014</td>
</tr>
<tr>
<td>Compilation of feedback</td>
<td>April 2014</td>
</tr>
<tr>
<td>Discussion at informal consultation on Specifications for The International Pharmacopoeia and laboratory standards in Geneva</td>
<td>3–4 April 2014</td>
</tr>
<tr>
<td>Event Description</td>
<td>Date/Details</td>
</tr>
<tr>
<td>----------------------------------------------------------------------------------</td>
<td>---------------------------------------</td>
</tr>
<tr>
<td>Compilation of feedback to IAEA</td>
<td>May 2014</td>
</tr>
<tr>
<td>Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>13–17 October 2014</td>
</tr>
<tr>
<td>Update during the fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>12–16 October 2015</td>
</tr>
<tr>
<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>
</tr>
<tr>
<td>IAEA update during the fifty-first WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>17–21 October 2016</td>
</tr>
<tr>
<td>Review and discussion during informal consultation on quality control laboratory tools and specifications for medicines</td>
<td>2–4 May 2017</td>
</tr>
<tr>
<td>IAEA delegated final review and modifications to Professor Alain Nicolas, France</td>
<td>May–September 2017</td>
</tr>
<tr>
<td>Mailing of revised monograph for public consultation</td>
<td>September 2017</td>
</tr>
<tr>
<td>Presentation to the fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
<td>16–20 October 2017</td>
</tr>
<tr>
<td>Any further action as necessary</td>
<td></td>
</tr>
</tbody>
</table>
Monograph for Sodium pertechnetate ($^{99m}$Tc) injection (fission)
(Natrii pertechnetatis ($^{99m}$Tc) fissione formati injectio)

This monograph applies to sodium pertechnetate ($^{99m}$Tc) injection obtained from generators containing molybdenum-99 ($^{99}$Mo) extracted from fission products of uranium.

Latin. Natrii pertechnetatis ($^{99m}$Tc) fissione formati injectio

English. Sodium pertechnetate ($^{99m}$Tc) injection (fission)

Structural formula

\[
\begin{align*}
\text{Na}^+ & \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
& \quad \begin{array}{c}
\text{Tc} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array} \\
& \quad \begin{array}{c}
\text{O} \\
\text{O} \\
\text{O} \\
\text{O}
\end{array}
\end{align*}
\]

Molecular formula. Na$^{99m}$TcO$_4$

Relative molecular mass. 185.99

Chemical name. Sodium oxido(trioxo)technetium-99m

Other name. Sodium tetraoxotechnetate (VII)

Description. Sodium pertechnetate ($^{99m}$Tc) injection (fission) is a clear, colourless solution. Technetium-99m has a half-life of 6.02 hours.

Category. Diagnostic.

Labelling. The label complies with the General monograph Radiopharmaceuticals.

Manufacture

Sodium pertechnetate is produced in $^{99}$Mo/$^{99m}$Tc generator by the radioactive decay of parent radionuclide molybdenum-99. The latter is formed as a fission by-product of $^{235}$Uuranium. The specific activity of fission-produced $^{99}$Mo molybdenum is very high in comparison to that of (non-fission)-produced. The produced $^{99}$Mo is loaded onto a chromatographic column of alumina which allows separation of $^{99m}$TcO$_4$ using a suitable $^{99}$Mo/$^{99m}$Tc generator system. A sterile solution of 0.9% sodium chloride may be used to elute under aseptic conditions.
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

Sodium pertechnetate ($^{99m}$Tc) injection (fission) is a sterile solution containing technetium-99m in the form of pertechnetate ion, suitable for intravenous administration. It contains sufficient sodium chloride to make the solution isotonic. The injection contains not less than 90% and not more than 110% of the declared technetium-99m radioactivity stated on the label at the reference date and time. Not less than 95% of the total technetium-99m radioactivity is present as pertechnetate ion. Technetium-($^{99m}$Tc) which is resulted from the decay of fission $^{99}$Mo parent radionuclide should meet the specifications with respect to the fission products as shown in following table.

<table>
<thead>
<tr>
<th>Radionuclidic impurity</th>
<th>Limit (per cent/total radioactivity)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molybdenum-99</td>
<td>$10^{-1}%$</td>
</tr>
<tr>
<td>Iodine-131</td>
<td>$5\times10^{-3}%$</td>
</tr>
<tr>
<td>Ruthenium-103</td>
<td>$5\times10^{-3}%$</td>
</tr>
<tr>
<td>Strontium-89</td>
<td>$6\times10^{-2}%$</td>
</tr>
<tr>
<td>Strontium-90</td>
<td>$6\times10^{-6}%$</td>
</tr>
<tr>
<td>Alpha-emitting impurities</td>
<td>$1\times10^{-7}%$</td>
</tr>
<tr>
<td>Other gamma-emitting impurities</td>
<td>$1\times10^{-4}%$</td>
</tr>
</tbody>
</table>

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, solution is 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 distribution of radioactivity in the preparation.

Tests

pH. Perform the test as described under 1.13 Determination of pH or R1.5 under the monograph for Radiopharmaceuticals.

The pH of the injection should be between 4.0 and 8.0

Aluminium

Test solution. In a test tube about 12 mm in internal diameter, mix 1 mL of acetate buffer solution pH 4.6 R and 2 mL of a 1 in 2.5 dilution of the preparation to be examined in water R. Add 0.05 mL of a 10 g/L solution of chromazurol S R.

Reference solution. Prepare at the same time and in the same manner as the test solution and using 2 mL of aluminium standard solution (2 ppm Al) R.

After 3 minutes, the colour of the test solution is not more intense than that of the reference solution.

The concentration of the aluminium ion in the injection is not greater than 5 µg per mL.

Sterility. The 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 product 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.

Radionuclidic purityMolybdenum-99 (impurity B) and other gamma-emitting impurities.

Molybdenum-99 and other gamma-emitting impurities can be determined by gamma-ray spectrometry. Molybdenum-99 is the principal radionuclidic impurity in test solution. It needs to be determined only for first elution of $^{99}$Mo/$^{99m}$Tc generators.

Retain a sample of the preparation to be examined for a sufficient time to allow the technetium-99m radioactivity to decay to a sufficiently low level to permit the detection of radionuclidic impurities. All measurements of radioactivity are expressed with reference to the date and time of administration.
Molybdenum-99 (Impurity B)

Record the gamma-ray spectrum of the decayed material. The most prominent gamma photons have energies of 0.181 MeV, 0.740 MeV and 0.778 MeV; molybdenum-99 has a half-life of 66.0 h. Compare the radioactivity with that of a standardized molybdenum-99 solution.

The radioactivity due to Molybdenum-99 (Impurity B) does not exceed 0.1% of the total radioactivity of the test solution.

Other gamma-emitting impurities

Examine the gamma-ray spectrum of the decayed material for the presence of other radionuclidic impurities, which should, where possible, be identified and quantified.

The total radioactivity due to other gamma-emitting impurities does not exceed 0.01% of the total radioactivity of the test solution.

Iodine-131 (Impurity A). Record the gamma-ray spectrum using a suitable instrument calibrated with the aid of a standardized iodine-131 solution and measure the half-life using a suitable method. Iodine-131 exhibits major peak of 365 keV and a half-life of 8.06 days. Not more than $5 \times 10^{-3}$% of the total radioactivity is due to iodine-131.

Ruthenium-103 (Impurity C). Record the gamma-ray spectrum using a suitable instrument calibrated with the aid of a standardized of ruthenium-103 solution and measure the half-life using a suitable method. Ruthenium-103 exhibits a major peak of 497 keV and a half-life of 39.3 days. Not more than $5 \times 10^{-3}$% of the total radioactivity is due to ruthenium-103.

Strontium-89 (Impurity D). The existence of strontium-89 in the injection is determined by using a suitable calibrated counting instrument for the detection of beta rays. An initial chemical separation may be required. Strontium-89 decays by beta emission with a maximum energy of 1.491 MeV and a half-life of 50.5 days. Not more than $6 \times 10^{-5}$% of the total radioactivity is due to strontium-89.

Strontium-90 (Impurity E). The existence of strontium-90 in the injection is estimated by using a suitable calibrated counting instrument for the detection of beta rays. Strontium-90 exhibits a major peak of maximum 546 keV and a half-life of 29.1 years. Not more than $6 \times 10^{-6}$% of the total radioactivity is due to strontium-90.

Alpha-emitting impurities. Record the alpha-ray spectrum using a suitable instrument, measure the half-life using a suitable method and determine the relative amount of alpha-emitting impurities. Not more than $1 \times 10^{-7}$% of the total radioactivity is due to alpha-emitting impurities which should, where possible, be identified and quantified.
Radiochemical purity

Either Method A or Method B to be applied.

Not less than 95% due to Technetium-99m as $[^{99m}\text{Tc}]$ pertechnetate ion.

Method A. Perform the test as described under 1.14.2 Paper chromatography and ascending conditions, using paper for chromatography R. A mixture of methanol R and water R (80:20, v/v) to be used as a mobile phase. The injection to be examined is used as a test solution, and is diluted with water or saline (0.9% sodium chloride w/v solution), to a suitable radioactive concentration. Apply to the paper about 5 μL of the test solution. Develop for 90 minutes and allow the paper to dry in air. Determine the radioactivity distribution by scanning using a radiochromatogram scanner with a collimator suitably adjusted to measure $[^{99m}\text{Tc}]$ or cut into 1 cm sections and count in a well type NaI(Tl) scintillation counter and corrected for background counts. In this system, $[^{99m}\text{Tc}]$ pertechnetate ion has an Rf value of about 0.6.

Method B. Perform the test as described under 1.14.2 Paper chromatography and ascending conditions, using Whatman No 1 paper strip R. Use acetone or methyl ethyl ketone as a mobile phase. The injection to be examined is used as test solution, and is diluted with water or saline (0.9% sodium chloride w/v solution) to a suitable radioactive concentration. Apply 2 to 5 μL of the test solution at 1 cm above the bottom of the strip. Run the chromatogram up to a distance of 6 cm. The Rf value for $[^{99m}\text{Tc}]$ pertechnetate ion is 0.9–1.0 and Rf value for reduced hydrolysed $^{99m}\text{Tc}$ is 0.0–0.1. The chromatographic strip is dried in air. Determine the radioactivity distribution by scanning using a radiochromatogram scanner with a collimator suitably adjusted to measure $^{99m}\text{Tc}$ or cut into two equal sections at 4.0 cm. The upper half section (section A) and bottom half section (section B) are counted separately in counting tubes in NaI(Tl) scintillation counter and corrected for background counts. Radiochemical purity is calculated as:

\[
\text{per cent RCP} = \frac{\text{Counts in section A}}{\text{Counts in section A} + \text{Counts in section B}} \times 100
\]

Radioactivity

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

Impurities

A. Iodine-131,
B. Molybdenum-99,
C. Ruthenium-103,
D. Strontium-89,
E. Strontium-90.