



Monograph for Sodium pertechnetate (^{99m}Tc) injection (fission)
(Natrii pertechnetatis (^{99m}Tc) fissione formati injectio)
(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 bonnyvw@who.int) and we will add it to our electronic mailing list.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.729

Sodium pertechnetate (^{99m}Tc) injection (fission)
 (Natrii pertechnetatis (^{99m}Tc) fissione formati injectio)

	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

42

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	

43

44

45

46

47

Monograph for Sodium pertechnetate (^{99m}Tc) injection (fission)

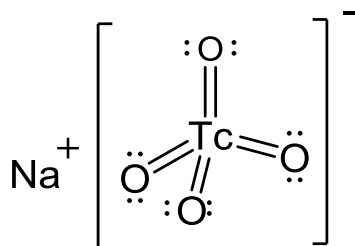
(Natrii pertechnetatis (^{99m}Tc) fissionis formati injectio)

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) fissionis formati injectio

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

Structural formula



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

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 $^{99}\text{Mo}/^{99m}\text{Tc}$ generator by the radioactive decay of parent radionuclide molybdenum-99. The latter is formed as a fission by-product of [^{235}U]uranium. 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 [$^{99m}\text{TcO}_4$] using a suitable $^{99}\text{Mo}/^{99m}\text{Tc}$ 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.

Radionuclidic impurity	Limit (per cent/total radioactivity)
Molybdenum-99	$10^{-1}\%$
Iodine-131	$5 \times 10^{-3}\%$
Ruthenium-103	$5 \times 10^{-3}\%$
Strontium-89	$6 \times 10^{-5}\%$
Strontium-90	$6 \times 10^{-6}\%$
Alpha-emitting impurities	$1 \times 10^{-7}\%$
Other gamma-emitting impurities	$1 \times 10^{-2}\%$

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 purity Molybdenum-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 $^{99}\text{Mo}/^{99\text{m}}\text{Tc}$ 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}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}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}Tc] pertechnetate ion has an R_f 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 R_f value for (^{99m}Tc) pertechnetate ion is 0.9–1.0 and R_f value for reduced hydrolysed ^{99m}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}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.
