World Health Organization

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

(Technetii (^{99m}Tc) succimeri multiplex 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 bonnyw@who.int) and we will add it to our electronic mailing list.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.735

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

(Technetii (^{99m}Tc) succimeri multiplex injectio)

Latin. Technetii (^{99m}Tc) succimeri multiplex injectio.

English. Technetium (^{99m}Tc) succimer complex injection.

Chemical name. (2*R*,3*S*)-2,3-disulfanylbutanedioic acid complexed with [^{99m}Tc] technetium (III).

Other names. (^{99m}Tc)-meso-2,3-dimercaptosuccinic acid complex injection; (^{99m}Tc)-DMSA injection, ^{99m}Tc-Succimer, Technetium-99m-DMSA, Technetium- [^{99m}Tc] succimer, ^{99m}Tc(III)-DMSA

Description. Technetium (^{99m}Tc) succimer complex injection is a clear, colourless aqueous solution.

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

Category. Diagnostic.

Storage. Technetium (^{99m}Tc) succimer complex injection is kept in single-dose containers, at a temperature between 15 °C and 30 °C and should be protected from light.

Labelling. The label complies with the General monograph *Radiopharmaceuticals*. (Note: A beyond-use time of 30 minutes shall be stated on the label upon constitution with Sodium Pertechnetate (^{99m}Tc) injection).

Manufacture

Technetium (^{99m}Tc) succimer complex injection is prepared aseptically from sterile starting materials such as a sterile kit containing *meso*-2,3-dimercaptosuccinic acid (DMSA) and a 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 chelating, stabilizing, filling, antioxidants such as ascorbic acid, and inert additives as well as antimicrobial preservatives and buffers. (^{99m}Tc) DMSA is prepared in acidic pH and the oxidation state of ^{99m}Tc is 3+ in this complex, otherwise its biological behavior will be different. The injection may also be prepared under aseptic processing combined with sterilization by filtration (see *5.8 Methods of sterilization*). The Technetium (^{99m}Tc) DMSA injection should be used within 4 hours from the stated date and time of 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) succimer complex injection, is a sterile solution of Sodium pertechnetate (^{99m}Tc) injection (Fission) or Sodium Pertechnetate (^{99m}Tc) injection (Non-fission) complexed with *meso*-2,3-dimercaptosuccinic acid (DMSA) that is present in excess. 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 95.0% of the total technetium-99m radioactivity is present as technetium (^{99m}Tc) succimer complex. The injection contains a variable quantity of tin (Sn) not greater than 1 mg/mL.

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 Technetium (^{99m}Tc) DMSA.

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 2.3 and 3.5.

Tin. Carry out the test as described under *R2.1.4 Tin estimation by UV absorption*, using 1.0 mL of a test solution prepared by diluting 1.5 mL of the injection to be examined to 25.0 mL with hydrochloric acid (103 g/L) VS and mixing thoroughly. Prepare the reference solution by dissolving 0.115 g of stannous chloride R using a solution in hydrochloric acid R (103 g/L HCl) and dilute to 1000.0 mL using the same acid. To the test solution and to 1.0 mL of the reference solution add 0.05 mL of thioglycollic acid R, 0.1 mL of dithiol reagent R, 0.4 mL of a 20 g/L solution of sodium laurilsulfate R, 3.0 mL of 21 g/L solution of hydrochloric acid R. Mix and measure the absorbance of each solution at 540 nm using 21 g/L solution of hydrochloric acid as

a compensation liquid. The absorbance of the test solution is not greater than that of the reference solution; not more than 1 mg of Sn per mL.

Biodistribution

Perform the test as described under *R3.1 Biological distribution* using three rats each weighing 150–250 g. Inject each of the three rats with a volume not greater than 0.2 mL and containing not more than 0.1 mg of dimercaptosuccinic acid intravenously in a caudal vein or a saphenous vein. Euthanize the rats 1 hour after the injection. Remove the kidneys, the liver, the spleen, the stomach, the lungs and, if a caudal vein has been used for the injection, the tail. Using a suitable instrument determine the radioactivity in these organs.

In not fewer than two of the three rats used, the radioactivity in the kidneys is not less than 40%, and that in the liver is not more than 10.0%, that in the lungs is not more than 5.0% and that in the stomach is not more than 2.0%.

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 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

Either test 1 or test 2 to be applied

Test 1. Perform the test as described under *1.14.2 Paper chromatography* and ascending conditions using paper for chromatography R. Two strips of Whatman No 1 (size 1 x 8 cm) are used. The solvent to be used is acetone. Spot about 2–5 µL of ^{99m}Tc(III)-DMSA injection at 1 cm from one end of the strip in duplicate.

Develop the chromatogram until the solvent front reaches 6 cm from the point of spotting. Cut the strip into 2 sections; the lower half (0–3 cm) and the upper half (3–6 cm) and count in a well-type scintillation counter. Free pertechnetate impurity (impurity A) has a Rf of 0.9–1.0 in the upper half.

The percentage of activity in the ^{99m}Tc-pertechnetate zone should not be more than 2.0% of the total activity. The radiochemical purity of ^{99m}Tc(III)-DMSA (Rf = 0.0 - 0.1) should not be less than 95.0%.

Test 2. Perform the test as described under *1.14.1 Thin-layer chromatography*, using silica gel for chromatography R as the coating substance. Heat the plate at 110 °C for 10 minutes. Apply to the plate about 5 µL of the injection to be examined, suitably diluted to give an optimum count rate. Develop immediately for a distance of about 10 cm with methyl ethyl ketone R. Allow the plate to dry in air and determine the radioactivity distribution by a suitable method. In this system, the technetium ^{99m}Tc(III)-DMSA complex has a Rf value of 0.0–0.1 and the (^{99m}Tc)pertechnetate ion has a Rf value of 0.9–1.0. Not less than 95.0% of the total technetium-99m radioactivity is present as ^{99m}Tc(III)-DMSA. Not more than 2.0% of the total technetium-99m radioactivity is present as (^{99m}Tc)pertechnetate ion (impurity A).

Radioactivity

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

Impurities

A. [^{99m}Tc] pertechnetate ion.

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