Monograph for Technetium (\(^{99m}\text{Tc}\)) tetrofosmin complex injection
(Technetii (\(^{99m}\text{Tc}\)) tetrofosmini multiplex injectio)
(Sepember 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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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.732

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<td>3–7 December 2012</td>
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<td>Follow up by IAEA, including review of comments received</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>
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<td>IAEA update during the fifty-first WHO Expert Committee on Specifications for Pharmaceutical Preparations</td>
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<td>Review and discussion during informal consultation on quality control laboratory tools and specifications for medicines</td>
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<td>IAEA delegated final review and modifications to Professor Alain Nicolas, France</td>
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Monograph for Technetium ($^{99m}$Tc) tetrofosmin complex injection

(Technetii ($^{99m}$Tc) tetrofosmini multiplex injectio)

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

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

Structural formula

![Structural formula image]

Molecular formula. $C_{36}H_{80}O_{10}P_4^{99m}$Tc

Relative molecular mass. 895.88

Chemical name. 2-[bis(2-ethoxyethyl)phosphany]ethyl-bis(2-ethoxyethyl)phosphane; dioxotechnetium-99

Other names. Myoview

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

Category. Diagnostic.

Storage. Technetium ($^{99m}$Tc) tetrofosmin complex injection is kept in adequately shielded single-dose or multiple-dose containers at a temperature not more than 25°C.

Labelling. The label complies with the General monograph Radiopharmaceuticals.

Manufacture

Technetium ($^{99m}$Tc) tetrofosmin complex injection is prepared aseptically from sterile starting materials such as a sterile kit containing 1,2-bis[bis(2-ethoxyethyl)phosphino]ethane 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 stabilizing and
antioxidizing agents as well as 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) tetrofosmin complex injection is a sterile solution of 1,2-bis[bis(2-ethoxyethyl)phosphino]ethane (tetrofosmin) that is present in excess complexed with Sodium pertechnetate ($^{99m}$Tc) injection (Fission) or Sodium Pertechnetate ($^{99m}$Tc) injection (Non-fission), in the presence of a stannous salt or other suitable reducing agent. 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 technetium ($^{99m}$Tc) tetrofosmin 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 Technetium ($^{99m}$Tc) tetrofosmin in the preparation.

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 7.5 to 9.0.

Tin. Perform 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 each of the test solution and the reference
solutions (1.0 mL) 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.

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 before release of the preparation for use.
Carry out 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

Perform the test described under 1.14.1 Thin-layer chromatography and ascending conditions.
Apply 10–20 μL of the injection to be examined, suitably diluted to give an optimum count rate,
about 1.0 cm from the bottom of (2 ×20 cm) instant thin-layer chromatographic silica-gel strip
(ITLC-SG) R. Allow the spot to air-dry. Use a mixture of acetone and dichloromethane (35:65
V/V) as a mobile phase and develop the chromatogram to a distance of 15 cm. Allow the
chromatogram to dry in air and determine the radioactivity distribution by scanning with a
suitable radiation detector. The technetium (99mTc) tetrofosmin complex has a Rf value of about
0.5, the pertechnetate ion has a Rf value of 0.9 to 1.0 and reduced hydrolyzed technetium-99m
has a Rf value of about 0.0 to 0.1. The sum of the percentages of radioactivity corresponding to
the pertechnetate ion (Impurity B) and reduced hydrolysed technetium-99m (Impurity A) is not
more than 10%. Not less than 90% of the total technetium-99m radioactivity is present as
technetium (99mTc) tetrofosmin complex.

Radioactivity

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

Impurities

A. [99mTc]technetium in colloidal form;
B. [99mTc]pertechnetate ion.

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