World Health Organization

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

(Technetii (^{99m}Tc) medronati 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/17.731

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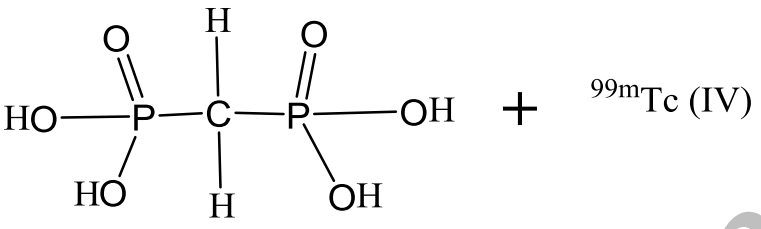
(Technetii (^{99m}Tc) medronati multiplex injectio)

Latin. Technetii (99mTc) medronati multiplex injectio

English. Technetium (99mTc) medronate complex injection

Structural formula



+ ^{99m}Tc (IV)

Medronoic acid:(MDP: $CH_6O_6P_2$)

Chemical name: Methylenebis(phosphonic acid)

Other names. (^{99m}Tc)-Methylene diphosphonate complex injection, (^{99m}Tc)-MDP injection.

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

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

Category. Diagnostic.

Storage. Technetium (^{99m}Tc) medronate complex injection should be kept at a temperature between 2 °C to 8 °C.

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

Manufacture

Technetium (^{99m}Tc) medronate complex injection is prepared aseptically from sterile starting materials such as a sterile kit containing sodium methylene diphosphonate 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) medronate complex injection is a sterile solution of sodium methylene diphosphonate (sodium medronate) that is complexes with technetium-99m, in 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% stated on the label at the reference date and time. Not less than 95% of the total technetium-99m radioactivity is present as technetium (^{99m}Tc) medronate complex. The injection contains a variable quantity of tin (Sn) not greater than 3 mg/mL *[**Note from the Secretariat:** suggestion to amend to* 3 mg/V*]*.

Identity tests

• Either tests A, C and D or tests B, C and D 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. Examine the radiochromatograms obtained in the test for Radiochemical purity. The retardation factor of the principal peak in the radiochromatogram obtained with the test solution in test 1 (system A) is 0.0 and in (system B) is 1.0.

D. Thin-layer chromatography. The injection may be released for use before completion of the test.

Test solution. Dilute the preparation to be examined with water R to obtain a solution containing about 0.1 mg/mL of medronic acid.

Reference solution (a). Dissolve 3 mg of sodium oxidronate R in water R and dilute to 10 mL with the same solvent.

Reference solution (b). Dissolve 1 mg of medronic acid R in water R and dilute to 10 mL with the same solvent.

Plate: cellulose for chromatography R as the coating substance.

Mobile phase: to 30 mL of water R add 35 mL of ethanol (96 per cent) R, 15 mL of 2-methylpropanol R, 0.4 mL of concentrated ammonia R, 5 g of trichloroacetic acid R and 20 mL of 2-propanol R and mix.

Application: about 5 µL, applied in 1 µL portions with drying after each application.

Development: over 2/3 of the plate.

Drying: in air for at least 14 hours.

Detection: spray with a solution prepared as follows: to 25 mL of a 40 g/L solution of ammonium molybdate R add 63 mL of water R, 2 mL of hydrochloric acid R, 2 mL of sulfuric acid R and 8 mL of perchloric acid R and mix. Expose the plate to ultraviolet light at 254 nm for 15 minutes.

System suitability: the retardation factor of the spot in the chromatogram obtained with reference solution (b) is about 0.6 and clearly different from that obtained with reference solution (a), which is about 0.5.

Results: the principal spot in the chromatogram obtained with the test solution is similar in position and colour to the principal spot in the chromatogram obtained with reference solution (b).

pH. Carry out the test as described under *1.13 or R1.5 Determination of pH* under the monograph for *Radiopharmaceuticals*, the pH value of the injection, should be between 3.5 and 7.5.

Tin. Determine the content of tin using a semi-quantitative tin test kit R, following the instructions given by the test kit manufacturer. If necessary, dilute the preparation to be examined with water R to obtain a concentration of tin within the measurement range of the test kit.

Not more than 3 mg of Sn per mL *[**Note from the Secretariat:** suggestion to amend to* 3 mg/V*]*.

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.

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 mL.

Radiochemical purity

Perform the test as described under *1.14.1 Thin-layer chromatography* using two separate systems: system (A) and system (B). Silica gel R to be used as the coating substance and methyl ethyl ketone R (system A) or sodium acetate (1 mol/L) VS (system B) as the mobile phase. Apply to the plates about 5 µL of the injection to be examined, suitably diluted to give an optimum count rate and develop for a distance of about 10 cm. Allow the plates to dry and determine the radioactivity distribution by a suitable method.

In system (A) the technetium (^{99m}Tc) medronate complex and reduced hydrolysed technetium-99m have a Rf value of 0.0–0.1 and the pertechnetate ion has a Rf value of 0.9–1.0.

In system (B) the technetium (^{99m}Tc) medronate complex and the pertechnetate ion have an Rf value of 0.9–1.0 and reduced hydrolysed technetium-99m has an Rf value of 0.0–0.1.

The sum of the percentages of radioactivity corresponding to the pertechnetate ion (Impurity B) in system (A) and reduced hydrolysed technetium-99m (Impurity A) in system (B) is less than 5% of the total radioactivity due to technetium-99m. Not less than 95% of the total technetium-99m radioactivity is present as technetium (^{99m}Tc) medronate complex.

Radioactivity

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

Impurities

A. [^{99m}Tc]technetium in colloidal form
B. [^{99m}Tc]pertechnetate ion.

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