World Health Organization

Monograph for Strontium (^{89}Sr) chloride injection (Strontii (^{89}Sr) chloridi injectio)

(January 2018)

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 Mrs Xenia Finnerty (finnertyk@who.int) by **16 March 2018.**

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/18.749

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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 (ECSPP)	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 ECSPP	13–17 October 2014
Update during the fiftieth WHO ECSPP	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 ECSPP	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–January 2018
Mailing of revised monograph for public consultation	January 2018
Following recommendation by the 52nd WHO ECSPP finalization of the monograph text, in accordance with the procedure, for publication in the 8th edition of *The International Pharmacopoeia* (2018), provided no major issues arise	March–April 2018
Presentation to the fifty-third ECSPP	22–26 October 2018
Any further action as necessary	

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(Strontii (^{89}Sr) chloridi injectio)

Latin. [^{89}Sr] Strontii chloridi injectio

English. [^{89}Sr] Strontium chloride injection

Structural formula

$$Cl^{-}.....^{89}Sr^{++}.....Cl^{-}$$

Molecular formula. $Cl_2{}^{89}Sr$

Relative molecular mass. 159.9

Chemical name. [^{89}Sr]strontium dichloride

Other names. Metastron, Strontium-89 chloride

Description. [^{89}Sr]Strontium chloride injection is a clear, colourless solution.

Strontium-89 has a half-life of 50.53 days.

Category. Therapeutic.

Storage. [^{89}Sr] Strontium chloride is stored at controlled room temperature (15 °–25 °C).

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

Manufacture

Strontium-89 is produced by neutron irradiation of strontium enriched in strontium-88.

The injection may be sterilized by "Heating in an autoclave" or it may 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

[^{89}Sr]Strontium chloride injection is a sterile solution of strontium-89 as strontium dichloride in presence of an excess of chloride ions, suitable for intravenous administration, and that contains sufficient sodium chloride to make the solution isotonic. The injection contains not less than 90% and not more than 110% of the content of strontium-89 stated on the label at the reference date and time. Not less than 99% of the total radioactivity is due to strontium-89. The specific activity is 2.96 to 6.17 MBq per mg of strontium at the reference date and time stated on the label. Not more than 0.6% of the total radioactivity is due to radionuclides other than strontium-89. The injection contains 6.0 mg per mL to 12.5 mg per mL of strontium.

Identity tests

A. Record the beta-ray spectrum using a suitable instrument with a sample of strontium-89, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of strontium-89 in that it exhibits a major peak of 1495 keV. Record the gamma-ray spectrum using a suitable instrument. The gamma photon detected has an energy of 909 keV and is due to the short-lived daughter product, yttrium-89m (formed in 0.01% of the disintegrations), in equilibrium with strontium-89.

B. The half-life determined using a suitable detector system is between 48 and 53 days.

C. A reddish-brown precipitate is formed after 1 minute when 0.1 mL of the injection to be examined is added with 1 mL of a freshly prepared 1 g/L solution of sodium rhodizonate R.

D. A white precipitate is formed when 0.1 mL of a 17 g/L silver nitrate solution is added to 50 µL of the injection to be examined.

pH value

Perform the test as described under *R1.5 or 1.13 Determination of pH* under the monograph for *Radiopharmaceuticals*, pH of the injection from 4.0 to 7.5.

Chemical purity

Aluminium

Perform the test as described under *1.8 Atomic spectrometry: emission and absorption*.

[Note: The standard preparation preparations and test preparation may be modified, if necessary, to obtain solutions of suitable concentrations adaptable to the linear or working range of the instrument].

The standard preparations and test preparation should be prepared at the same time and the same conditions. In this test, nitric acid is used as a diluent, which is prepared by diluting 40 mL of concentrated nitric acid with 1000 mL of distilled water R. Place 1.0 mL of injection to be

examined in a 100 mL volumetric flask and carefully add 4.0 mL of nitric acid R. Then dilute the resulting solution with distilled water R to the volume.

The standards (0.01, 0.02, and 0.04 µg per mL, respectively) are prepared by diluting aluminium solution (10 ppm Al) R using nitric acid diluent R.

Record the atomic emission spectrum for the standard solutions and the test solution at the aluminium emission line at 309.3 nm with an atomic absorption spectrophotometer equipped with an aluminium hollow-cathode lamp and a flameless electrically heated furnace using nitric acid diluent as blank. Plot the absorbance of the standard preparations versus the contents of Al, in µg per mL. From the graph determine the quantity, in µg, of Al in each mL of the test solution.

Not more than 2 µg/mL of the test preparation exists as aluminium.

Iron

Perform the test of as described under *1.8 Atomic spectrometry: emission and absorption*.

In this test, nitric acid R (4%, v/v) is used as diluent. Prepare the test solution by diluting 0.2 mL of the preparation to be examined using diluted nitric acid R to a suitable volume. The reference solutions are prepared by diluting iron solution (20 ppm Fe) R using nitric acid diluent R.

Record the atomic emission spectrum for the standard solutions and the test solution with an atomic absorption spectrophotometer using nitric acid diluent as blank. Plot the absorbance of the standard preparations versus the contents of iron, in µg per mL. From the graph determine the quantity, in µg, of iron in each mL of the test solution.

Not more than 5 µg/mL of the test preparation exists as iron.

Lead

Perform the test of as described under *1.8 Atomic spectrometry: emission and absorption*.

In this test, nitric acid R (4%, v/v) is used as diluent. Prepare the test solution by diluting 0.2 mL of the preparation to be examined using dilute nitric acid R to a suitable volume. The reference solutions are prepared by diluting lead solution (10 ppm Pb) R using nitric acid diluent R.

Record the atomic emission spectrum for the standard solutions and the test solution with an atomic absorption spectrophotometer, using nitric acid diluent as blank. Plot the absorbance of the standard preparations versus the contents of lead, in µg per mL. From the graph determine the quantity, in µg, of lead in each mL of the test solution.

Not more than 5 µg/mL of the test preparation exists as lead.

Strontium

Perform the test of as described under *1.8 Atomic spectrometry: emission and absorption*.

In this test, nitric acid R (4%, v/v) is used as diluent. Prepare the test solution by diluting 0.2 mL of the preparation to be examined using dilute nitric acid R to a suitable volume. Prepare the reference solutions using strontium standard solution (1.0% strontium) R diluted as necessary with nitric acid R.

Record the atomic emission spectrum for the standard solutions and the test solution at strontium emission line of 407.8 nm with an atomic absorption spectrophotometer using nitric acid diluent as blank. Plot the absorbance of the standard preparations versus the contents of strontium, in mg per mL. From the graph determine the quantity, in mg, of strontium in each mL of the test solution.

Content: 6.0 mg/mL to 12.5 mg/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

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

Gamma-emitting impurities other than yttrium-89m. [Note: Use a plastic container to perform the following test.] Record the gamma- and X-ray spectra using a suitable calibrated counting instrument and measure the half-life using a suitable method. Determine the relative amount of gamma-emitting impurities. Not more than 0.4% of the total radioactivity is due to gamma-emitting radionuclides other than yttrium-89m.

Beta-emitting impurities. The following test is used to determine the percent. of (sulphur-35 and phosphorus-32) in the preparation.

Using a column with 5–6 mm in diameter, packed with approximately 2 mL of cation exchange resin (100–250 µm), previously conditioned with dilute hydrobromic acid (7.9 g/L). Evaporate to dryness 100 µL of the preparation to be examined under a radiant heat source. Dissolve the residue in 2 mL of 47% hydrobromic acid R, evaporate to dryness under the radiant heat source and dissolve the residue in 2 mL of dilute hydrobromic acid (7.9 g/L). Transfer the solution to the top of the column. Elute the column with the same solvent until 10 mL of eluate has been collected into a container containing 50 µL of a 15 g/L solution of anhydrous sodium sulfate R in 1 M hydrochloric acid.

To a liquid scintillation cocktail vial add an appropriate volume of liquid scintillation cocktail (commercially available solution for the determination of radioactivity by liquid scintillation counting) followed by 1 mL of water R, 0.1 mL of a 15 g/L solution of anhydrous sodium sulfate R in 1 M hydrochloric acid and 100 µL of eluate. Shake to obtain a clear solution. Using suitable counting calibrated equipment determine the radioactivity due to sulphur-35 (impurity A) and phosphorus-32 (impurity B).

Not more than 0.2% of the total radioactivity is due to beta-emitting impurities.

Radioactivity

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

Impurities

A. Sulfur-35,
B. Phosphorus-32.

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