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Document for comment

World Health Organization

THE INTERNATIONAL PHARMACOPOEIA

RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

THALLOSI (^{201}Tl) CHLORIDI INJECTIO
THALLOUS (^{201}Tl) CHLORIDE INJECTION
(March 2014)

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopps@who.int; fax: (+41 22) 791 4730 (kopps@who.int) and to Ms Marie Gaspard (gaspardm@who.int), by 22 April 2014.

Working documents are sent out electronically and they will also be placed on the Medicines website for comment. If you do not already receive directly our draft guidelines 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/13.549
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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

Compilation of feedback to IAEA	May 2014
Any further action as necessary	
Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations	13–17 October 2014

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Monographs: Radiopharmaceuticals: Specific monographs: Thallosi (^{201}Tl) chloridi injectio - Thallous (^{201}Tl) chloride injection

Latin. Thallosi (^{201}Tl) chloridi injectio

English. Thallous (^{201}Tl) chloride injection

Structural formula. $^{201}Tl^{+}$..... Cl^{-}

Empirical formula. $^{201}TlCl$

Relative molecular mass. 236.423

Chemical name. [^{201}Tl]Thallium chloride

Other names. Thallous (^{201}Tl) chloride

Description. Thallous (^{201}Tl) chloride injection is a clear colourless, aqueous solution.

Thallium-201 has a half-life of 72.96 hours.

Category. Diagnostic.

Storage. After aseptic withdrawal of the first dose from a multidose container, the container should be stored at a temperature between 2 °C to 8 °C.

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

Manufacture

No-carrier-added thallium-201 radioisotope is produced by proton bombardment of enriched thallium 203 target followed by chemical separation of radioactive lead 201 isotope. The lead-201 isotope has a half-life of 9.4 hours and decays to thallium 201. Separation of thallium-201 may be done using anion-exchange resin chromatography or solvent extraction. Thallous (^{201}Tl) chloride injection may be sterilized by "Heating in an autoclave" (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. Thallous (^{201}Tl) chloride injection is a sterile, isotonic, aqueous solution of thallium-201 as thallous chloride, suitable for intravenous administration. It contains sufficient sodium chloride to make the solution isotonic with blood and may contain suitable antimicrobial preservatives such as benzyl alcohol or stabilizing agents. The injection contains not less than 90% and not more than 110% of the content of thallium-201 at the reference date and time stated on the label. Not less than 97% of the total radioactivity is due to thallium-201. Not more than 2% of the total radioactivity is due to thallium-202. The specific activity is not less than 3.7 GBq of thallium-201 per milligram of thallium at the reference date and time stated on the label.

Identity tests

• Either tests A and C or tests B and C may be applied.

A. Record the gamma-ray using a suitable instrument with a sample of thallium-201, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of thallium-201 in that it exhibits major peaks of 135, 166 and 167 keV and X-rays of 69 and 83 keV.

B. The half-life determined using a suitable detector system is between 69.31 and 76.6 hours.

C. Examine the radiochromatogram obtained in the test for radiochemical purity. Not less than 95% of the radioactivity present as [^{201}Tl]Thallium chloride and migrates on the strip towards the cathode as a single peak.

pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for Radiopharmaceuticals. The pH of the injection is between 4.0 and 7.0.

Sterility. The injection complies with 3.2 Test for sterility, modified as described in the monograph for Radiopharmaceuticals. Test for sterility will be initiated on the day of manufacture. The injection may be released for use before completion of the test.

Bacterial endotoxins. 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). The injection may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray and X-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of thallium-200, thallium-201, thallium-202, lead-201, lead 203 and other radionuclidic impurities that may be present. Thallium-202 has a half-life of 12.2 days and exhibits a main peak of 440 keV. Thallium-200 has a half-life of 1.09 days and exhibits main peaks of 368, 579, 828 and 1206 keV. Lead-201 has a half-life of 9.4 hours and exhibits a main peak of 331 keV. Lead-203 has a half-life of 2.17 days and exhibits a main peak of 270 keV. Not less than 97% of the total radioactivity is due to thallium-201. Not more than 2% of the total radioactivity is due to thallium-202.

Standardized solutions of thallium-201 and thallium-202 are available from laboratories recognized by the relevant national or regional authority.

Radiochemical purity. Carry out the test as described under 1.15 Electrophoresis, zone-electrophoresis. Prepare a suitable cellulose polyacetate strip as the supporting medium and soak the strip in a solution of disodium edetate R (18.6 g/L) as the electrolyte solution. Soak the strip in the electrolyte solution for 45–60 min. Remove the strip with forceps, taking care to handle the outer edges only. Place the strip between 2 absorbent pads and blot to remove excess solution. Apply not less than 5 µl of a mixture of equal volumes of the preparation to be examined and the electrolyte solution to the centre of the

blotted strip and mark the point of application. Attach the strip to the support bridge of an electrophoresis chamber containing equal volumes of disodium edetate R in each side of the chamber. Ensure that each end of the strip is in contact with the disodium edetate R. Apply an electric field of 250 volts per metre for 30 minutes. Allow the strip to dry in air. Determine the distribution of radioactivity using suitable detector.

Not less than 95% of the radioactivity on the strip migrates towards the cathode as a single peak.

Chemical purity

Thallium. Transfer 1.0 ml of the injection and 1.0 ml of thallium standard (2 µg/ml Tl) TS to separate screw-cap test tubes. To each tube add the following five solutions (A, B, C, D and E) and mix after each addition: 2 drops of a solution prepared by carefully mixing 18 ml of nitric acid (~1000 g/l) TS and 82 ml of hydrochloric acid (~250 g/l) TS (solution A); 1.0 ml of sulfosalicylic acid (0.1 mol/l) VS (solution B); 2 drops of hydrochloric acid (~250 g/l) TS (solution C); 4 drops of a solution prepared by dissolving 50 mg of rhodamine B R in hydrochloric acid (~250 g/l) TS and diluting to 100.0 ml (solution D); 1.0 ml of diisopropyl ether R (solution E). Screw the caps on tightly, shake the tubes by hand for exactly 1 minute, releasing any pressure build-up by loosening the caps slightly. Recap the tubes and allow the phases to separate. Transfer 0.5 ml of the ether layer from each tube to clean tubes. The colour of the ether layer obtained from the injection is not darker than that from the thallium standard (2 µg/ml Tl) TS.

Iron. Into separate cavities of a spot plate place 0.1 ml of the injection and 0.1 ml of iron standard TS diluted with water R to a concentration of 5 µg/ml. Add to each cavity 0.1 ml of a solution of hydroxylamine hydrochloride R (1 in 10), 1 ml of a solution of sodium acetate R (1 in 4) and 0.1 ml of a 0.5% dipyridyl solution prepared by dissolving 0.5 g of 2,2'-dipyridyl R in 100 ml of water R containing 0.15 ml of hydrochloric acid (~250 g/l) TS and mix. After 5 minutes the colour obtained from the injection is not darker than that of the iron standard solution.

Copper. Into separate cavities of a spot plate place 0.2 ml of the injection and 0.2 ml of copper standard (5 µg/ml Cu) TS. Add to each cavity the following 3 solutions (A, B and C) and mix after each addition: 0.2 ml of water R (solution A) and 0.1 ml of a solution of iron thiocyanate prepared by dissolving 1.5 g of ferric chloride R and 2 g of potassium thiocyanate R in water R and diluting to 100.0 ml with the same solvent (solution B); 0.1 ml of a solution of sodium thiosulphate R (1 in 100) (solution C). The time required for the injection to decolorize is equal to or longer than that observed for the copper standard solution.

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

Impurities

A. Lead-201,

B. Lead-203,

C. Thallium-200,

D. Thallium-202,

E. [^{201}Tl] Thallic (III) ion.

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