

### THE INTERNATIONAL PHARMACOPOEIA 1 RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH 2 THALLOSI (201Tl) CHLORIDI INJECTIO 3 THALLOUS (201TI) CHLORIDE INJECTION 4 (March 2014) 5 6 7 REVISED DRAFT FOR COMMENT 8 Should you have any comments on the attached text, please send these to Dr Sabine Kopp, Group 9 Lead, Medicines Quality Assurance, Technologies, Standards and Norms, World Health Organization, 1211 Geneva 27, Switzerland; email: kopps@who.int; fax: (+41 22) 791 4730 10 (kopps@who.int) and to Ms Marie Gaspard (gaspardm@who.int), by 22 April 2014. 11 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 12 have your email address (to bonnyw@who.int) and we will add it to our electronic mailing list. 13 14 15 16 © World Health Organization 2014 17 All rights reserved. 18 This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft 19 may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any 20 form or by any means outside these individuals and organizations (including the organizations' concerned staff and member

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# SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.549 THE INTERNATIONAL PHARMACOPOEIA RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH THALLOSI (201 TI) CHLORIDI INJECTIO THALLOUS (201 TI) CHLORIDE INJECTION

	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
	Soft Continue the
	Any further action as necessary  Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations

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52	THE INTERNATIONAL PHARMACOPOEIA
53	RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH
54	THALLOSI ( <sup>201</sup> Tl) CHLORIDI INJECTIO
55	THALLOUS (201TI) CHLORIDE INJECTION
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57	Monographs: Radiopharmaceuticals: Specific monographs: Thallosi
58	( <sup>201</sup> Tl) chloridi injectio - Thallous ( <sup>201</sup> Tl) chloride injection
59	
	Latin Thallasi (2017) ablavidi inicati
60	Latin. Thallosi ( <sup>201</sup> Tl) chloridi injectio
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62	English. Thallous ( <sup>201</sup> Tl) chloride injection
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	Structural formula 201TI+Cl
64	Structural formula.
65	
66	Empirical formula. <sup>201</sup> TlCl
67	
	Relative molecular mass. 236.423
68	Relative molecular mass. 230,423
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70	Chemical name. [ <sup>201</sup> Tl]Thallium chloride
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72	Other names. Thallous ( <sup>201</sup> Tl) chloride
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	201700 11 11 201700 11 11 11 11 11 11 11 11 11 11 11 11 1
74	<b>Description.</b> Thallous ( <sup>201</sup> Tl) chloride injection is a clear colourless, aqueous solution.
75	Thallium-201 has a half-life of 72.96 hours.
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77	Category. Diagnostic.
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- 79 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.
- 81 Labelling. The label complies with the General monograph, the monograph of
- 82 Radiopharmaceuticals.

### Manufacture

- No-carrier-added thallium-201 radioisotope is produced by proton bombardment of
- 85 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.
- 87 Separation of thallium-201 may be done using anion-exchange resin chromatography or
- 88 solvent extraction. Thallous (<sup>201</sup>Tl) chloride injection may be sterilized by "Heating in an
- 89 autoclave" (see 5.8 Methods of Sterilization).

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### **Additional information**

- 92 Wherever V is used within the tests of this monograph, V is the maximum recommended
- 93 dose in millilitres.

# 94 Requirements

- 95 Complies with the monograph for Parenteral Preparations and with that for
- 96 Radiopharmaceuticals.
- 97 **Definition.** Thallous (<sup>201</sup>Tl) chloride injection is a sterile, isotonic, aqueous solution of
- 98 thallium-201 as thallous chloride, suitable for intravenous administration. It contains
- 99 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-
- 102 201 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 76.6 113 114 115 Examine the radiochromatogram obtained in the test for radiochemical purity. Not C. 116 less than 95% of the radioactivity present as [201Tl]Thallium chloride and migrates 117 on the strip towards the cathode as a single peak. 118 119 pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under 120 121 the monograph for Radiopharmaceuticals. The pH of the injection is between 4.0 and 7.0. 122 Sterility. The injection complies with 3.2 Test for sterility, modified as described in the 123 monograph for Radiopharmaceuticals. Test for sterility will be initiated on the day of 124 125 manufacture. The injection may be released for use before completion of the test. 126 Bacterial endotoxins. Carry out the test as described under 3.4 Test for bacterial 127 endotoxins, modified as described in the monograph for Radiopharmaceuticals. The 128 129 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. 130 131 Radionuclidic purity. Record the gamma-ray and X-ray spectrum using a suitable 132 133 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 134 135 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 136 exhibits main peaks of 368, 579, 828 and 1206 keV. Lead-201 has a half-life of 9.4 hours 137 and exhibits a main peak of 331 keV. Lead-203 has a half-life of 2.17 days and exhibits a 138 139 main peak of 270 keV. Not less than 97% of the total radioactivity is due to thallium-201. 140 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 141 recognized by the relevant national or regional authority. 142 143 Radiochemical purity. Carry out the test as described under 1.15 Electrophoresis, zone-144 145 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 146 solution. Soak the strip in the electrolyte solution for 45–60 min. Remove the strip with 147 forceps, taking care to handle the outer edges only. Place the strip between 2 absorbent 148 149 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.

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## **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,
- 162 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.

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- 173 **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.

- 181 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
- 183 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.
- 189 **Radioactivity.** Measure the radioactivity using a suitable instrument as described under
- 190 R.1.1 Detection and measurement of radioactivity.

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192	Impurities
193	A. Lead-201,
194	B. Lead-203,
195	C. Thallium-200,
196	D. Thallium-202,
197	E. [ <sup>201</sup> Tl] Thallic (III) ion.
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