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THE INTERNATIONAL PHARMACOPOEIA

2

RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

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NATRII IODIDI (¹³¹I) SOLUTIO SODIUM IODIDE (¹³¹I) SOLUTION

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(March 2014)

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REVISED DRAFT FOR COMMENT

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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.

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39 **SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.547**
 40 **THE INTERNATIONAL PHARMACOPOEIA**
 41 **RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH**
 42 ***NATRII IODIDI (¹³¹I) SOLUTIO***
 43 **SODIUM IODIDE (¹³¹I) SOLUTION**

	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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Revised draft for comment

**THE INTERNATIONAL PHARMACOPOEIA
RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH**

***NATRII IODIDI (^{131}I) SOLUTIO
SODIUM IODIDE (^{131}I) SOLUTION***

Monographs: Radiopharmaceuticals: Specific monographs: Natrii iodidi (¹³¹I) solutio - Sodium iodide (¹³¹I) solution

Latin: Natrii iodide (^{131}I) solutio.

English. Sodium iodide (^{131}I) solution.

Relative molecular mass, 153.895

Empirical formula. Na^{131}I

Chemical name. Sodium [^{131}I] iodide

Other names. Natriiradioiodidum, Iodotope Sodium iodide-I 131

Description. Sodium iodide (^{131}I) solution is a clear colourless solution.

Iodine-131 has a half-life of 8.02 days.

Category. Diagnostic or therapeutic.

Storage. Stored at room temperature in a single-dose or multiple-dose containers.

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

Manufacture. No carrier added iodine-131 may be obtained by neutron bombardment of tellurium or by extraction from uranium fission products.

Sodium iodide (^{131}I) solution may contain sodium thiosulfate, sodium hydrogen carbonate or other suitable reducing agents and may contain a suitable buffer.

Additional information. Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

Additional information. Wherever V is used within the tests of this monograph, V is the maximum recommended dose, in millilitres.

90 Requirements

91

92 Complies with the monographs for [Liquid preparations for oral use](#), [Parenteral Preparations](#) and
93 with that for [Radiopharmaceuticals](#) as and where appropriate.

94

95 **Definition.** Sodium iodide solution is an aqueous solution containing radioactive (^{131}I) in
96 the form of sodium iodide (^{131}I), suitable for either oral or intravenous administration.

97

98 The solution contains not less than 90% and not more than 110% of the declared
99 radioactivity due to iodine-131 stated on the label at the reference date and time. Not less
100 than 99.9% of the total radioactivity is due to iodine-131. Not less than 95% of the total
101 iodine-131 radioactivity is present as iodide. It contains minute amounts of naturally
102 occurring iodine 127. The specific activity is not less than 185 MBq per microgram of
103 iodine at the reference date and time stated on the label. The iodide content of maximum
104 recommended dose should not be more than 20 μg .

105

106 Identity tests

107

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

109

110 A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a
111 sample of iodine-131, suitably diluted if needed. The spectrum is concordant with
112 the *reference spectrum* of a specimen of iodine-131 in that it exhibits a major
113 peak of 365 keV. Standardized iodine-131 solutions are available from
114 laboratories recognized by the relevant national or regional authority.

115

116 B. The half-life determined using a suitable detector system is between 7.61 and 8.42
117 days.

118

119 C. Examine the radiochromatogram obtained in the test for radiochemical purity. The
120 principal peak in the chromatogram obtained with the test solution (a) is similar in
121 retention time to the principal peak in the chromatogram obtained with the
122 reference solution (c).

123

124 **pH value.** Carry out the test as described under [1.13 Determination of pH](#) or [R1.5](#) under
125 the monograph for [Radiopharmaceuticals](#). pH is between 7.0 and 10.0.

126

127 **Sterility.** The solution complies with [3.2.1 Test for sterility of non-injectable](#)
128 [preparations](#), modified as described in the monograph for [Radiopharmaceuticals](#). If
129 intended for intravenous administration, it complies with [3.2 Test for sterility](#) for
130 injectable preparations, modified as described in the monograph for
131 [Radiopharmaceuticals](#). The solution may be released for use before completion of the test.

132

133

134

135

136 **Bacterial endotoxins**

137

138 Carry out the test as described under [3.4 Test for bacterial endotoxins](#), for solution
139 intended for intravenous use modified as described in the monograph for
140 [Radiopharmaceuticals](#). The injection contains not more than 175/V (I.U of endotoxins per
141 millilitre).

142

143 **Radionuclidic purity.** Record the gamma-ray and X-ray spectrum using a suitable
144 instrument and measure the half-life using a suitable method. Determine the relative
145 amounts of iodine-131, iodine-133, iodine-135 and other radionuclidic impurities that
146 may be present. Iodine-133 has a half-life of 20.8 hours and exhibits major peaks of
147 530 keV and 875 keV. Iodine-135 has a half-life of 6.57 hours and exhibits major peaks
148 of 527 keV, 1132 keV and 1260 keV. Not less than 99.9% of the total radioactivity is due
149 to iodine-131.

150

151 **Chemical purity**

152

153 **Iodide.** Carry out the test as described under [1.14.4 High-performance liquid](#)
154 [chromatography](#), using a stainless steel column (0.25 m x 4.0 mm) packed with particles
155 of silica gel, the surface of which has been modified with chemically-bonded
156 octadecylsilyl groups (5 µm), maintain the temperature constant between 20 °C and
157 30 °C. Dissolve 5.844 g of sodium chloride R in 1000 mL of water R, add 650 µL of
158 octylamine R and adjust to pH 7.0 with phosphoric acid R, add 50 mL of acetonitrile R
159 and mix. Use the mixture as the mobile phase. Use flow rate of 1.5 mL/min, and
160 spectrophotometer detector at 220 nm and radioactivity detector (connected in series) for
161 detection. Prepare the test solution (a) which is the preparation to be examined. Prepare
162 the test solution (b) by diluting test solution (a) using 0.05 M sodium hydroxide until the
163 radioactivity is equivalent to about 74 MBq/mL and add an equal volume of a solution
164 containing 1 g/L of potassium iodide R, 2 g/L of potassium iodate R and 10 g/L of
165 sodium hydrogen carbonate R and mix. The reference solution (c) is prepared by diluting
166 1 mL of a 26.2 mg/L solution of potassium iodide R to V with water R, (V being the
167 *maximum recommended dose in millilitres*). Prepare the reference solution (d) by dilution
168 1 mL of a 24.5 mg/L solution of potassium iodate R to V with water R, (V being the
169 *maximum recommended dose in millilitres*). Mix equal volumes of this solution and of
170 reference solution (c). Prepare a solution containing 2 mg/mL of each of the components
171 stated on the label, apart from iodide, used as blank solution. Inject 25 µL of test solution
172 (a), the blank solution and reference solutions (c) and (d). The run time is 12 minutes.
173 The relative retention of iodate with reference to iodide (retention time of iodide is about
174 5 minutes): iodate is from 0.2 to 0.3.

175

176 **System suitability.** Regarding the chromatogram due to the blank solution, none of the
177 obtained peaks shows a retention time similar to that of the peak due to iodide. The
178 resolution is a minimum of 2 between the peaks due to iodide and iodate in the
179 chromatogram obtained with reference solution (d) recorded with the spectrophotometer.

180

181 The limit of iodide is detected by studying the chromatogram obtained with the
182 spectrophotometer and comparing the peak due to iodide with the chromatogram due to
183 reference solution (c). The area of the peak due to iodide is not more than the area of the
184 corresponding peak in the chromatogram obtained with reference solution (c).

185

186 Radiochemical purity

187

- 188 • **Either test A, B, or C may be applied**

189

190 A. Carry out the test as described under [1.14.2 Paper chromatography](#) and ascending
191 conditions, using paper for chromatography R (25 × 300 mm). Place a measured
192 volume of a solution containing 100 mg of potassium iodide, 200 mg of
193 potassium iodate and 1 g of sodium bicarbonate, and 25 mm from one end of the
194 chromatographic paper. Allow the paper to dry. To the same area of the paper add
195 an equal volume of appropriately diluted solution such that it provides a count rate
196 of about 20 000 counts per minute and allow the paper to dry. Develop the
197 chromatogram over a period of about 4 hours by ascending chromatography,
198 using dilute methanol (7:10, v/v). Allow the paper to dry in air and determine the
199 radioactivity distribution by scanning with a suitable radiation detector: the
200 radioactivity of the [¹³¹I]iodide band is not less than 95% of the total radioactivity
201 and its *R_F* value falls within ±5% of the value found for sodium iodide when
202 determined under parallel conditions. Confirmation of the identity of the iodide
203 band is made by the addition to the suspected iodide band of 6 drops of acidified
204 hydrogen peroxide solution (prepared by adding 6 drops of 1 N hydrochloric acid
205 to 10 mL of hydrogen peroxide solution), followed by the dropwise addition of
206 starch TS; the development of a blue color indicates presence of iodide.

207

208 B. Carry out the test [1.14.4 High-performance liquid chromatography](#) as described in
209 the test for iodide with the following modification:
210

- 211 • inject test solution (b),
- 212 • using the chromatogram obtained with the radioactivity detector, determine the
213 radioactivity of the peak for iodide as a percentage of the total radioactivity. Not
214 less than 95% of the total radioactivity is due to [¹³¹I] iodide.

215

216 B. Carry out the test as described under [1.15 Electrophoresis, Paper-electrophoresis](#)
217 Prepare paper strips, type Whatman No. 3 MM for electrophoresis with
218 dimensions of 65 cm × 3 cm. Apply 10–20 µL samples at a distance of 10–13 cm
219 from the end of the stripes. Use borate buffer with a concentration of 9.0 g/L and
220 pH 9.0 ± 0.1. Carry out the electrophoresis at a potential of 900 V for 50 minutes.
221 The R_f values for iodide are between 0.7 and 0.9, R_f for iodate is 0.4, periodate
222 from 0.0 to 0.1. The product can be accepted if the ¹³¹I anion content is higher
223 than 95% even on the expiry date.

224

225 **Radioactivity.** Measure the radioactivity using a suitable instrument as described under
226 [R.1.1 Detection and measurement of radioactivity](#).

227

228 **Impurities**

229

230 $[^{131}\text{I}]$ iodate ion.

231

232

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Revised draft for comment