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Document for comment

World Health Organization

THE INTERNATIONAL PHARMACOPOEIA

RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

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

(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/13.547
THE INTERNATIONAL PHARMACOPOEIA
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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: Natrii iodidi (^{131}I) solutio - Sodium iodide (^{131}I) solution

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

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

Structural formula. $Na^{+}\cdots\cdots{}^{131}I^{-}$

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.

Requirements

Complies with the monographs for Liquid preparations for oral use, Parenteral Preparations and with that for Radiopharmaceuticals as and where appropriate.

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

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

Identity tests

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

A. Record the gamma-ray and X-ray spectrum using a suitable instrument with a sample of iodine-131, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of iodine-131 in that it exhibits a major peak of 365 keV. Standardized iodine-131 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 7.61 and 8.42 days.

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

pH value. Carry out the test as described under 1.13 Determination of pH or R1.5 under the monograph for Radiopharmaceuticals. pH is between 7.0 and 10.0.

Sterility. The solution complies with 3.2.1 Test for sterility of non-injectable preparations, modified as described in the monograph for Radiopharmaceuticals. If intended for intravenous administration, it complies with 3.2 Test for sterility for injectable preparations, modified as described in the monograph for Radiopharmaceuticals. The solution 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, for solution intended for intravenous use modified as described in the monograph for Radiopharmaceuticals. The injection contains not more than 175/V (I.U of endotoxins per millilitre).

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 iodine-131, iodine-133, iodine-135 and other radionuclidic impurities that may be present. Iodine-133 has a half-life of 20.8 hours and exhibits major peaks of 530 keV and 875 keV. Iodine-135 has a half-life of 6.57 hours and exhibits major peaks of 527 keV, 1132 keV and 1260 keV. Not less than 99.9% of the total radioactivity is due to iodine-131.

Chemical purity

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

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

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

Radiochemical purity

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

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

B. Carry out the test 1.14.4 High-performance liquid chromatography as described in the test for iodide with the following modification:

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

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

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

227
228 **Impurities**
229
230 [^{131}I] iodate ion.
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