World Health Organization

Monograph for Sodium (^{125}I) iothalamate (Natrii (^{125}I) iothalamatis 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.

© World Health Organization 2018

All rights reserved.

This draft is intended for a restricted audience only, i.e. the individuals and organizations having received this draft. The draft may not be reviewed, abstracted, quoted, reproduced, transmitted, distributed, translated or adapted, in part or in whole, in any form or by any means outside these individuals and organizations (including the organizations' concerned staff and member organizations) without the permission of the World Health Organization. The draft should not be displayed on any website.

Please send any request for permission to:

Dr Sabine Kopp, Group Lead, Medicines Quality Assurance, Technologies Standards and Norms, Department of Essential Medicines and Health Products, World Health Organization, CH-1211 Geneva 27, Switzerland. Fax: (41-22) 791 4730; email: kopps@who.int.

The designations employed and the presentation of the material in this draft do not imply the expression of any opinion whatsoever on the part of the World Health Organization concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by the World Health Organization in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by the World Health Organization to verify the information contained in this draft. However, the printed material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall the World Health Organization be liable for damages arising from its use.

This draft does not necessarily represent the decisions or the stated policy of the World Health Organization.

Draft for comment

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/18.752

Monograph for Sodium (^{125}I) iothalamate
(Natrii (^{125}I) iothalamatis injectio)

	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

Draft for comment

41

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	

Draft for comment

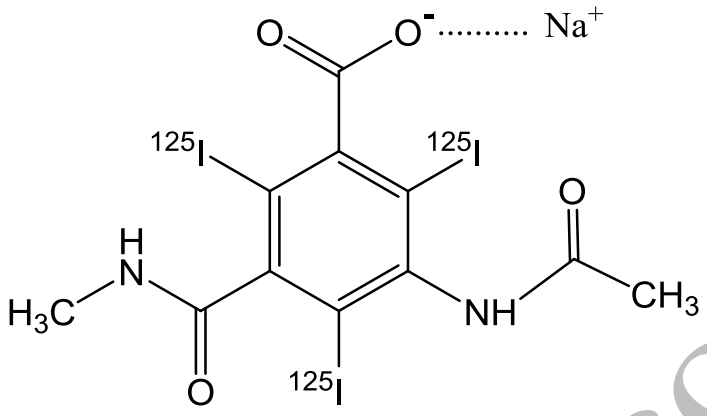
42
43
44
45
46
47

Monograph for Sodium (^{125}I) iothalamate
(Natrii (^{125}I) iothalamatis injectio)

Latin. Natrii [^{125}I]iothalamatis injectio

English. Sodium [^{125}I]iothalamate injection

Structural formula



Molecular formula. $C_{11}H_8{}^{125}I_3N_2NaO_4$

Relative molecular mass. 630.184

Chemical name. Sodium 3-(acetylamino)-2,4,6-tri[^{125}I]iodo-5-(methylcarbamoyl)benzoate; sodium 5-(acetylamino)-2,4,6-tri[^{125}I]iodo-*N*-methylisophthalamate.

Other names. Sodium [^{125}I]iothalamate injection, GLOFIL-125, iothalamate sodium (I-125) injection.

Description. Sodium [^{125}I]iothalamate injection is a clear, colourless aqueous solution. Iodine-125 has a half-life of 59.4 days.

Category. Diagnostic

Storage. Sodium [^{125}I]iothalamate injection should be kept at a temperature between 2 °C to 8 °C, protected from light.

Labelling. The label complies with the General monograph of *Radiopharmaceuticals*. The label states the date of withdrawal of the first dose for multidose containers.

Manufacture

Iodine-125 is obtained in a reactor by neutron irradiation of xenon.

Draft for comment

Sodium [^{125}I]iothalamate is generally prepared by exchange labelling. The injection may have the pH adjusted with sodium bicarbonate and may contain stabilizing and filling agents as well as antimicrobial preservatives and buffers. The injection may also 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

Sodium [^{125}I]iothalamate injection is a sterile solution of iodine-125 in the form of iothalamic acid in water for injection prepared with the aid of sodium bicarbonate R, suitable for intravenous administration and that contains sufficient sodium chloride to make the solution isotonic. A portion of the molecules of iothalamate will contain iodine-125 in molecular structure. Sodium [^{125}I]iothalamate injection contains not less than 90% and not more than 110% of the content of iodine-125 stated on the label at the reference date and time. Not less than 95% of the total radioactivity is due to iodine-125. Not less than 98% of the total iodine-125 radioactivity is present as iothalamate.

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-125, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of iodine-125 in that it exhibits a major peak of 27 keV, corresponding to the X-ray of tellurium. Iodine-126 has a half-life of 13.0 days and main peaks of 388 keV and 666 keV.

Standardized iodine-125 and caesium-137 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 55 and 65 days.

C. Examine the radiochromatogram obtained in the test for radiochemical purity: Not less than 98% of the total iodine-125 radioactivity is in the spot corresponding to iothalamate.

Draft for comment

pH

Perform the test as described under *R1.5* or *1.13 Determination of pH* under the monograph for *Radiopharmaceuticals*, pH of the injection should be from 7.0 to 8.5.

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

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-125, iodine-126 and other radionuclidic impurities that may be present, on the assumption that the 666 keV gamma photon of iodine-126 is emitted in 33% of disintegrations and that the 661 keV gamma photon of caesium-137 is emitted in 85.4% of disintegrations. Not less than 95% of the total radioactivity is due to iodine-125. Not more than 1% of the total radioactivity is due to iodine-126.

Radiochemical purity

Perform the test as described under *1.14.2 Paper chromatography* and ascending conditions, using paper (25 × 300 mm) for chromatography R. Use as mobile phase a mixture of methanol and ammonium hydroxide (100:1.5, V/V), adjusted with 1 M sulfuric acid (100 g/L) TS to pH 3–6. Apply to the paper 10 µL of the injection to be examined, suitably diluted to give an optimum count rate (20 000 counts per minute). Develop the chromatogram (over a period of about 4 hours) for a distance of 20 cm. Allow the paper to dry in the air and determine the radioactivity distribution with a suitable collimated radiation detector. In this system iothalamate has an Rf value of about 0.0 and free iodine-125 has an Rf value of about 0.9–1.0. Not more than 2% of the total iodine-125 radioactivity is in the spot corresponding to free iodine-125. Not less than 98% of the total iodine-125 radioactivity is in the spot corresponding to iothalamate.

Radioactivity

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

Impurities

Iodine-126

***

Draft for comment