World Health Organization

Monograph for [^{123}I] Iobenguane injection ([^{123}I] Iobenguani 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.

SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/18.750

Monograph for [^{123}I] Iobenguane injection
([^{123}I] Iobenguani 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

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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	

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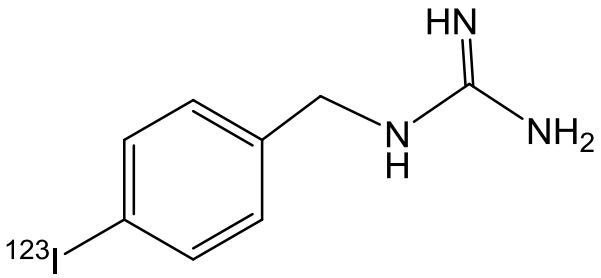
Latin. [^{123}I] Iobenguani injectio

English. [^{123}I] Iobenguane injection

Structural formula



[Note from the Secretariat: The formula will be corrected to change from substitution in position 4 to position 3 as stated in the chemical name.]

Molecular formula. $C_8H_{10}{}^{123}IN_3$

Relative molecular mass. 271.19

Chemical name. 1-((3-[^{123}I]iodophenyl)methyl)guanidine

Other names. m-[^{123}I]Iodobenzylguanidine injection; [^{123}I]-MIBG injection, Adreview®.

Description. [^{123}I]Iobenguane injection is a clear, colourless or slightly yellow aqueous solution. Iodine-123 has a half-life of 13.2 hours.

Category. Diagnostic.

Storage. [^{123}I] Iobenguane injection should be kept at a temperature between 2 °C to 8 °C, protected from light and during transportation, at a temperature below -10 °C.

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

Manufacture

Iodine-123 is obtained in a cyclotron by proton irradiation of xenon enriched in xenon-124 (not less than 98%), which decays to xenon-123 followed by the decay of caesium-123 formed via xenon-123 to iodine-123. [^{123}I]Iobenguane is generally prepared by isotope exchange reaction and the formulations contain large amounts of unlabelled iobenguane molecules. The injection may contain fillers, preservatives, buffers and stabilizing agents. [^{123}I]Iobenguane injection may

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

[^{123}I]Iobenguane injection is a sterile bacterial endotoxin-free aqueous solution of iodine-123 in the form of 1-((3-[^{123}I]iodophenyl)methyl)guanidine or its salts, suitable for intravenous administration and that contains sufficient sodium chloride to make the solution isotonic. The injection contains not less than 90% and not more than 110% of the content of iodine-123 stated on the label at the reference date and time. Not less than 95% of the total iodine-123 radioactivity is present as iobenguane. The specific activity is not less than 10 GBq of iodine-123 per gram of iobenguane base at the reference date and time stated on the label. Not more than 0.35% of the total radioactivity is due to radionuclides other than iodine-123.

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-123, suitably diluted if needed. The spectrum is concordant with the *reference spectrum* of a specimen of iodine-123 in that it exhibits a major peak of 159 keV.

Iodine-124 has a half-life of 4.2 days and a main peak of 603 keV. Iodine-125 has a half-life of 59.4 days and emits X-rays of 27 keV and a photon of 35 keV. Tellurium-121 has a half-life of 19.2 days and mains peaks of 507 and 573 keV.

Standardized iodine-123, iodine-125 and tellurium-121 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 12.54 and 13.86 hours.

C. Examine the radiochromatogram obtained in the test for radiochemical purity. The distribution of the radioactivity contributes to the identification of the preparation.

pH

Perform the test as described under *R1.5* or *1.13 Determination of pH* under the monograph for *Radiopharmaceuticals*, pH of the injection from 3.5 to 8.0

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

The preparation may be released for use before completion of the test.

Record the gamma-ray and X-ray spectrum using a suitable instrument. Determine the relative amounts of iodine-125, iodine-123, tellurium-121 and other radionuclidic impurities that may be present. Not more than 0.35% of the total radioactivity is due to other radionuclides than iodine-123 such as iodine-125 and tellurium-121. No radionuclides with a half-life longer than that of iodine-125 are detected. Retain the injection to be examined for a sufficient time to allow iodine-123 to decay to a level which permits the detection of radionuclidic impurities.

Radiochemical purity

Carry out the test as described under *1.14.4 High-performance liquid chromatography* using a stainless steel column (25 cm x 4.0 mm) packed with silica gel for chromatography R (5 µm). As the mobile phase use a mixture of 80 g/L solution of ammonium nitrate R, ammonia (~ 35 g/L) TS and methanol R (1:2:27 V/V/V). Operate with a flow rate of 1.0 mL/min. As a detector use detectors suitable for radioactivity and a spectrophotometer set at a wavelength of 254 nm. Prepare the following solutions: solution (1), use the injection to be examined. Solution (2), prepare 0.1% (w/v) solution of sodium iodide R in the mobile phase. Solution (3), prepare 0.02% (w/v) solution of iobenguane sulfate R in mobile phase (dissolve 20.0 mg of iobenguane sulfate R in 50 mL of the mobile phase and dilute to 100 mL with the mobile phase). Inject separately 10 µL of solutions (1), (2) and (3).

Record the chromatogram and measure the responses of the major peaks. In the obtained chromatogram; not less than 95% of the total radioactivity is in the peak corresponding to [^{123}I]Iobenguane. Not more than 4% of the total radioactivity corresponding to [^{123}I]iodine and not more than 1% of the total radioactivity is found in other peaks is due to the other impurities.

Specific radioactivity

The specific radioactivity is calculated from the results obtained in the test for radiochemical purity. Determine the content of iobenguane sulfate from the areas of the peaks due to iobenguane in the chromatograms obtained with solutions (1) and (3). Calculate the concentration as iobenguane base by multiplying the result obtained in the test by 0.85.

Radioactivity

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

Impurities

A. [^{123}I]iodide,
B. Iodine-125,
C. Tellurium-121.

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