



Monograph for (¹⁸F) Fludeoxyglucose injection
((¹⁸F) Fludeoxyglucosi injection)
(September 2017)

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 Ms Xenia Finnerty (finnertyk@who.int) by 1 November 2017.

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.

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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.

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SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/17.733Monograph for (¹⁸F) Fludeoxyglucose injection((¹⁸F) Fludeoxyglucosi 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

41

Compilation of feedback to IAEA	May 2014
Presentation to forty-ninth WHO Expert Committee on Specifications for Pharmaceutical Preparations	13–17 October 2014
Update during the fiftieth WHO Expert Committee on Specifications for Pharmaceutical Preparations	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 Expert Committee on Specifications for Pharmaceutical Preparations	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–September 2017
Mailing of revised monograph for public consultation	September 2017
Presentation to the fifty-second WHO Expert Committee on Specifications for Pharmaceutical Preparations	16–20 October 2017
Any further action as necessary	

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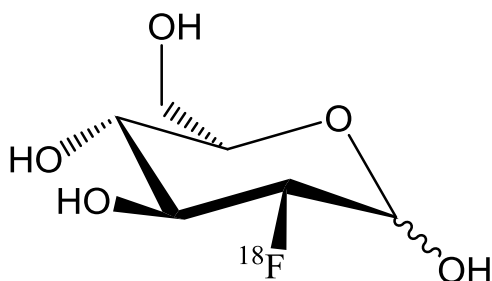
Monograph for (^{18}F) Fludeoxyglucose injection

((^{18}F) Fludeoxyglucosi injectio)

Latin. [^{18}F]Fludeoxyglucosi injectio

English. [^{18}F]Fludeoxyglucose injection

Structural formula



$\text{C}_6\text{H}_{11}^{18}\text{FO}_5$

Relative molecular mass. 181.1

Chemical name. 2-deoxy-2- ^{18}F fluoroglucose

Other names. ^{18}F -FDG injection, 2- ^{18}F fluoro-2-deoxy-D-glucopyranose, 2- ^{18}F fluoro-2-deoxy-D-glucose.

Description. [^{18}F]Fludeoxyglucose injection is a clear, colourless or slightly yellow solution; Fluorine-18 has a half-life of 109.8 minutes.

Category. Diagnostic.

Labelling. The label complies with the General monograph [Radiopharmaceuticals](#).

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

[^{18}F] Fludeoxyglucose injection is a sterile solution of [^{18}F]fluorine in the form of 2-[^{18}F]fluoro-2-deoxy-D-glucose, for intravenous administration and contains sufficient sodium chloride to make the solution isotonic. It contains not less than 90% and not more than 110% of [^{18}F]fluorine radioactivity stated on the label at the reference date and time. Not less than 99% [*Note from the Secretariat: suggestion to amend to 99.9%*] of the total radioactivity is due to [^{18}F]fluorine. Not less than 95% of the total [^{18}F]fluorine radioactivity is present as 2-[^{18}F]fluoro-2-deoxy-D-glucose and 2-[^{18}F]fluoro-2-deoxy-D-mannose, with the latter not exceeding 10% of the total radioactivity. The content of 2-fluoro-2-deoxy-D-glucose is not more than 0,5 mg/V.

Manufacture

The first step in the manufacture of [^{18}F]FDG is the production of [^{18}F]fluoride in a cyclotron through proton irradiation of oxygen-18 enriched water (target material). It may be also produced by deuteron irradiation of neon-20 or alpha irradiation of oxygen-16. 2-[^{18}F]fluoro-2-deoxy-D-glucose ([^{18}F]FDG) may be synthesized by a nucleophilic, electrophilic or solid-phase ^{18}F -fluorination pathway, which leads to different products in terms of specific activity, by-products and possible impurities. The [^{18}F]FDG radiopharmaceutical produced by nucleophilic substitution contains no carrier added [^{18}F]fluorine.

Starting material (precursor for organic synthesis)

1,3,4,6-Tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose (tetra-acetyl mannose triflate). This is a sugar molecule containing a suitable leaving group (triflate). Perform the test as described under [1.7 Spectrophotometry in the infrared region](#). The infrared absorption spectrum is concordant with the reference spectrum of 1,3,4,6-tetra-O-acetyl-2-O-trifluoromethanesulfonyl- β -D-mannopyranose.

Melting point range is from 119 °C to 122 °C.

Chemical synthesis (nucleophilic substitution)

2-[^{18}F]fluoro-2-deoxy-D-glucose is produced by nucleophilic reaction of [^{18}F]fluoride with (tetra-acetyl mannose triflate). [^{18}F] Fluoride is adsorbed on an anion-exchange resin and eluted with a solution of potassium carbonate, evaporated to dryness. To enhance the nucleophilicity of the [^{18}F]fluoride, a phase-transfer catalyst, such as aminopolyether (Kryptofix®) or tetra-butyl ammonium salt (TBA) soluble in dry acetonitrile at elevated temperature, may be used. The nucleophile [^{18}F]fluoride ion approaches the tetra-acetyl mannose triflate and displaces the triflate group. Final step of [^{18}F]FDG production is to remove acetyl protecting groups on 1,3,4,6 position carbons by either using acid hydrolysis or base hydrolysis. Depending on the conditions of hydrolysis, variable amounts of 2-chloro-2-deoxy-D-glucose and/or 2-[^{18}F]fluoro-2-deoxy-D-mannose may be formed as a by-product. The produced [^{18}F]FDG preparation can be purified by passing through a series of columns for removal of impurities. These columns could include cation exchange resin for removal of Kryptofix® or TBA, alumina for removal of unreacted

[¹⁸F]fluoride, and ion retardation resin for neutralization and pH adjustment. The injection is sterilized by an appropriate method depending on the class of environment where manufacturing is taking place (see [5.8 Methods of sterilization](#)).

Identity tests

A. Record the gamma-ray spectrum using a suitable instrument (calibrated multichannel analyser) with a sample of fluorine-18, suitably diluted if needed. The spectrum of [¹⁸F]fluorine should exhibit a major peak of 511 keV and sum peak of 1 022 keV may also be seen depending on geometry and detector efficiency.

B. The half-life determined using a suitable detector system is between 105 and 115 minutes.

C. Examine the radiochromatogram obtained in the test for radiochemical purity. Determine the distribution of radioactivity on a TLC strip that corresponds to [¹⁸F]FDG. The peak corresponding to [¹⁸F]FDG should have a R_f value of about 0.4 and should represent more than 95% of the total radioactivity.

pH. Perform the test as described under [1.13 Determination of pH](#) or [R1.5](#) under the monograph for [Radiopharmaceuticals](#). The pH of the injection should be between 4.5 and 8.5.

Chemical purity

Depending upon the method applied for the [¹⁸F]FDG production, chemical impurities may arise through procedures employed. These chemical impurities or by-products including aminopolyether, tetra-butyl ammonium salts and 2-chloro-2-deoxy-D-glucose, are to be controlled at appropriate limits. Particular tests which are employed for potential chemical impurities analysis and control may be omitted if the substances mentioned are not used or cannot be formed in the production process.

2-Fluoro-2-deoxy-D-glucose and 2-chloro-2-deoxy-D-glucose (impurity A). Perform the test of [1.14.4 High-performance liquid chromatography](#); the test is performed as described under the test of radiochemical purity. Prepare reference solutions (a), (b) and (c). The relative retention with reference to 2-fluoro-2-deoxy-D-glucose (retention time = about 12 minutes): 2-fluoro-2-deoxy-D-mannose = about 0.9; impurity A = about 1.1. In the chromatogram obtained with the carbohydrate detector the area of the peak corresponding to 2-fluoro-2-deoxy-D-glucose is not greater than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.5 mg/V). The area of the peak corresponding to impurity A is not greater than the area of the corresponding peak in the chromatogram obtained with reference solution (b) (0.5 mg/V).

Aminopolyether (Kryptofix®) (Impurity B). This test is performed only on the bulk solution before addition of sodium chloride by the producer and it is not intended for the final preparation to be injected. Perform the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel for chromatography R as the coating substance and a mixture of 30% ammonium hydroxide R and methanol R (10: 90, v/v) as the mobile phase. For solution (A) use the injection to be

examined. Solution (B) is the aminopolyether reference solution which is prepared in water at concentration of 0.22 mg/mL. Apply separately to the plate 2 μ L of each (solution A and solution B). Develop the plate for a distance of about 8 cm. After removing the plate from the chromatographic chamber allow it to dry in air for 15 minutes. Expose the plate to iodine vapour in a closed container containing iodine R crystals at the bottom for at least 10 minutes to visualize the spots. Examine the chromatogram in daylight..

Any spot due to aminopolyether in the chromatogram obtained with solution A is not more intense than the corresponding spot obtained with solution B (0.22 mg/mL).

Tetra-butyl ammonium salts (Impurity C). Perform the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (12.5 cm x 4.0 mm) packed with particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 μ m). As the mobile phase use a mixture of 25 volumes of a 0.95 g/L solution of toluenesulfonic acid R and 75 volumes of acetonitrile R. For solution (A) use the injection to be examined. For solution (B) dilute 2.1 mL of tetrabutylammonium hydroxide (0.1 mol/L) VS to 20 mL with water R. Dilute 1.0 mL of this solution to V with the same solvent. Operate with a flow rate of 1.0 mL per minute. As a detector use an ultraviolet spectrophotometer set at a wavelength of 254 nm. Inject separately 10 μ L each of solutions A and B. In the chromatogram obtained with solution A the area of the peak corresponding to tetrabutylammonium ions is not greater than that of the corresponding peak obtained with solution B (2.75 mg/V) [*Note from the Secretariat: suggestion to amend to 2.6 mg/V*].

Solid phase derivatization agent 4-(4-methylpiperidin-1-yl)pyridine (Impurity D). Measure the absorbance of the following solutions at the maximum of 263 nm. For solution (A) use the preparation to be examined. For solution (B) dissolve 20.0 mg of 4-(4-methylpiperidin-1-yl)pyridine R in water R and dilute to 100.0 mL with the same solvent. Dilute 0.1 mL of this solution to V with the same solvent. The absorbance obtained from solution A is not greater than the absorbance obtained from solution B (0.02 mg/V).

Residual solvents

Product may be released before completion of the test.

Perform the test as described under [1.14.5 Gas chromatography](#) using a (0.53 mm x 30 m) fused-silica column coated with 0.25 μ m, chemically cross-linked G16 stationary phase R. Use helium R as the carrier gas at a flow rate of 10 mL per minute. The gas chromatogram equipment includes flame-ionization detector and a splitless injector system. Maintain the injection port and the detector temperatures at 250 °C and 300 °C, respectively. Prepare standard solutions of ether, acetonitrile and dehydrated alcohol (concentrations of 0.1%, 0.01% and 0.1%, respectively). The preparation to be examined is used as the test solution. Initially the temperature is maintained at 40 °C for 2 minutes, then the temperature is increased at a rate of 20 °C per minute to 130 °C, and maintained at 130 °C for 5.5 minutes. Inject equal volumes (about 1 μ L) of the standard solutions and the test solution into the chromatograph, record the chromatograms, and measure the peak responses. Calculate the percentage of acetonitrile, ether and alcohol in the Injection by the formula:

$$C(r_i / r_s)$$

in which C is the percentage of the relevant analyte in the standard solution; and r_i and r_s are the peak responses of the relevant analyte obtained from the test solution (if any) and the standard solution, respectively: not more than 0.04% of acetonitrile is found; not more than 0.5% of ether is found; and not more than 0.5% of alcohol is found.

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

The injection complies with the test described under [3.2 Test for sterility](#), modified as described in the monograph for [Radiopharmaceuticals](#). Test for sterility will be initiated on the day of manufacture.

Bacterial endotoxins. The test must be completed before the release of the preparation.

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.

Membrane filter integrity test

This test must be completed before release of the drug product.

The sterility test of that product is completed retrospectively and it is required to perform an appropriate bubble point test on the membrane filter that is used for the terminal sterilization. The membrane filter integrity test does not replace the sterility test.

Radionuclidic purity. The preparation may be released for use before completion of test B.

- A. Record the gamma-ray emission spectrum of a sample collected from the preparation using an appropriate gamma spectrometer (for example, NaI(Tl)-based or semiconductor detector). The resultant gamma spectrum should be analysed for the presence of identifiable photo peaks which are not characteristic of ^{18}F emissions. Not less than 99.5% of the observed gamma emissions should correspond to the 0.511 MeV, 1.022 MeV, or Compton scatter peaks of ^{18}F . [*Note from the Secretariat: suggestion to amend to 99; 99.5 or 99.9 %*].
- B. Determine the amount of fluorine-18 and radionuclidic impurities with a half-life longer than 2 hours using gamma ray spectrometry. For the detection and quantification of impurities, retain the preparation to be examined for at least 24 hours allowing the fluorine-18 to decay to a level that permits the detection of impurities.

The total radioactivity due to radionuclidic impurities is not more than 0.1%

Radiochemical purity

Either test A or test B may be applied (The test must be completed before release of the product)

- A. Perform the test as described under [1.14.1 Thin-layer chromatography](#) using silica gel for chromatography R as the coating substance and a mixture of acetonitrile R: water R (95: 5 v/v) as the mobile phase. Prepare a reference solution by dissolving with gentle heating 30 mg of 1,2,3,4-tetra-O-acetyl- β -D-glucopyranose R and 20 mg of glucose R in 1 mL of water R. For the test solution use the injection to be examined. Apply separately to the plate 2 μ L of the test solution and reference solution. Develop the plate for a distance of about 8 cm. After removing the plate from the chromatographic chamber allow it to dry in air for 15 minutes. Determine the radioactivity distribution by using a suitable collimated radiation detector. Visualize fludeoxy glucose by immersing the plate in a 75 g/L solution of sulphuric acid R in methanol R and dry with heat gun or at 150 °C until the appearance of dark spots in the chromatogram obtained with the reference solution. R_f value of [¹⁸F]fluoride ion is 0.0, R_f value of 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose is about 0.4, and R_f value of partially or fully acetylated derivatives of 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose is about 0.8 to 0.95. Not less than 95% of total [¹⁸F]fluorine radioactivity is due to 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose. Not more than 5% of total [¹⁸F]fluorine radioactivity is due to fluoride and partially or fully acetylated derivatives of 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose.
- B. Perform the test as described under [1.14.4 High-performance liquid chromatography](#) using a stainless steel column (0.25 m x 4.6 mm) packed with strongly basic anion-exchange resin for chromatography R (10 μ m) as a stationary phase. The temperature is constant between 20 °C and 25 °C. The mobile phase to be used is 4 g/L solution of sodium hydroxide R in carbon dioxide-free water R. The flow rate is 1.0 mL/min. Use a detector suitable for carbohydrates in the required concentration range, such as pulse amperometric detector and radioactivity detector connected in series. Prepare reference solution (a) by dissolving 1.0 mg of 2-fluoro-2-deoxy-D-glucose R in water R and dilute to 2.0 mL with the same solvent. Dilute 1.0 mL of the solution to V with water R, V being the maximum recommended dose in millilitres. Reference solution (b) is prepared by dissolving 1.0 mg of 2-chloro-2-deoxy-D-glucose R (impurity A) in water R and dilute to 2.0 mL with the same solvent. Dilute 1.0 mL of the solution to V with water R, V being the maximum recommended dose in millilitres. Prepare reference solution (c) by dissolving 1.0 mg of 2-fluoro-2-deoxy-D-mannose R in water R and dilute to 20.0 mL with the same solvent. Mix 0.5 mL of this solution with 0.5 mL of reference solution (a). Inject 20 μ L of test solution and reference solutions (a) and (c). Relative retention with reference to 2-[¹⁸F]fluoro-2-deoxy-D-glucose (retention time = about 12 minutes): 2-[¹⁸F]fluoro-2-deoxy-D-mannose = about 0.9. Partially or fully acetylated derivatives of both compounds are hydrolysed under the chromatographic conditions and therefore eluted as 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose using the chromatogram (carbohydrate detection) and reference solutions (a) and (c). Minimum 95% of the total radioactivity due to fluorine-18 is due to 2-[¹⁸F]fluoro-2-deoxy-D-glucose and 2-[¹⁸F]fluoro-2-deoxy-D-mannose.

Maximum 10% of the total radioactivity due to 2-[^{18}F]fluoro-2-deoxy-D-glucose and 2-[^{18}F]fluoro-2-deoxy-D-mannose is due to 2-[^{18}F]fluoro-2-deoxy-D-mannose.

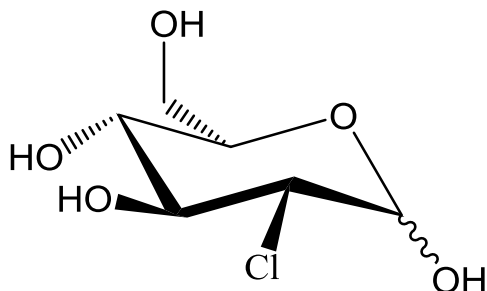
Radioactivity

Measure the radioactivity using suitable counting instrument as described under [R.1.1 Detection and measurement of radioactivity](#).

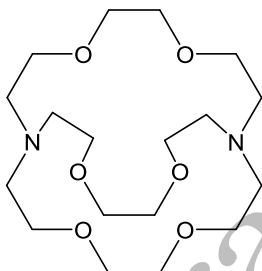
Impurities

Specified impurities: A, B, C, D, E.

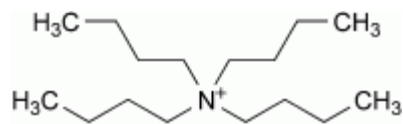
A. 2-chloro-2-deoxy-D-glucose (2-chloro-2-deoxy-D-glucopyranose),



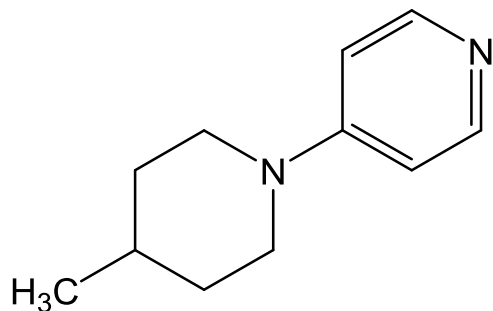
B. 4,7,13,16,21,24-hexaoxa-1,10-diazabicyclo[8.8.8]hexacosane (aminopolyether),



C. *N,N,N*-tributylbutan-1-aminium (tetrabutylammonium),



D. 4-(4-methylpiperidin-1-yl)pyridine,



E. [¹⁸F]fluoride.
