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Volume II - Monographs

Radiopharmaceuticals

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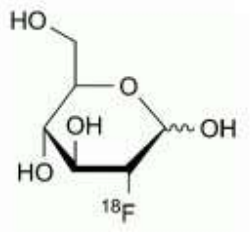
RADIOPHARMACEUTICALS

FLUDEOXYGLUCOSE (18 F), INJECTION

Fludeoxyglucosi (^{18}F) injectio



$C_6H_{11}{}^{18}FO_5$; 181.15
fludeoxyglucose (18 F); 04114
2-[^{18}F]fluoro-2-deoxy-D-glucopyranose (2-[^{18}F]fluoro-2-deoxy-D-glucose); 2-deoxy-2-[^{18}F]fluoro-Dglucose; FDG-^{18}F
[*105851-17-0*]

It contains not less than 90 percent and not more than 110 percent of fludeoxyglucose (18 F) radioactivity, at the date and time stated on the label

DESCRIPTION

Fludeoxyglucose (18 F) is a sterile, clear or slightly yellow solution of 2-deoxy-2-[18F]fluoro-D-glucose. It may contain preservative, stabilizing agents or buffering agents. Fluorine-18 (18 F) is positron-emitting radionuclide with half-life of 111 minutes. It may be prepared by proton irradiation of oxygen-18 (18 O) in cyclotron accelerators and processed in a manner that 18 F obtained is carrier free.

IDENTIFICATION

A. *Radionuclidic identity*: proceed according to *Radiopharmaceuticals* (8.3). The physical half-life of 18 F determined using a suitable detector system, is between 105 and 115 minutes. In the gamma-ray spectrum obtained in the Radionuclidic purity test, the gamma emissions must correspond to the 0.511 MeV peak and also to the 1.022 MeV sum peak, depending on the measurement geometry.

B. *Radiochemical identity*: the Rf value of fludeoxyglucose (18 F) on the chromatogram of the *Sample solution* must correspond to the chromatogram of the *Standard solution*, as obtained in *the Radiochemical purity test.*

PURITY TESTS

pH (5.2.19). 4.5 to 7.5.

Radiochemical purity. Carry out of the test as described in *Thin-layer chromatography* **(5.2.17.1)**. *Standard solution*: dissolve 10 mg of fludeoxyglucose (non-radioactive 2-deoxy-2-fluoro-D-glucose; MW 182.15) CRS in 100 mL of acetonitrile:water (95:5).

Sample solution: fludeoxyglucose (18 F) injection to be analyzed.

Stationary phase: activated chromatographic silica gel TLC-plate with adequate dimensions.

Mobile phase: acetonitrile: water (95:5).

Procedure: Place an aliquot of the diluted Sample solution in order to obtain an adequate counting rate for the radioactivity detection system. Approximately 10 µL of the Standard solution is applied on the same TLC-plate. Develop the chromatogram until the mobile phase has moved about ¾ of the length of the plate. Remove the plate and allow it to air-dry. Determine the radioactivity distribution on the plate with a suitable radiation detector.

In order to determine the position of fludeoxyglucose, spray the chromatographic plate with 1 M sulfuric acid solution, followed by heating until a spot appears. The Rf value of the Sample solution corresponds to that of the Standard solution (approximately 0.4). At least, 90 % of the total radioactivity correspond to fludeoxyglucose (18 F).

Chemical purity.

Note*: the methods and limits described in this section are related to potential impurities that are associated to the synthesis process. The following tests are not necessary when those specific substances are not used or generated in the synthesis process.*

Aminopolyether limit. Carry out the test as described in *Thin-layer chromatography* **(5.2.17.1)**.

Sample solution: fludeoxyglucose (18 F) injection to be analyzed.

Standard solution: weigh the appropriate amount of aminopolyether (4,7,13,16,21,24-hexaoxa-1,10diazabicyclp[8.8.8]hexacosane) CRS and dissolve in 0.9 % sodium chloride solution (w/v) to obtain solution at 50 µg/mL.

Stationary phase: chromatographic silica gel TLC-plate.

Mobile phase: methanol:ammonium hydroxide 30% (9:1).

Procedure: Separately apply about 2.5 µL of the Sample solution and the Standard solution on the TLC-plate. Develop the chromatogram. Remove the plate and let it dry at room temperature. Place the plate in a chamber containing iodine crystals until a spot is visible on the chromatogram of the Standard solution.

The size and intensity of the aminopolyether spot of the *Sample solution* must not exceed that of the *Standard solution.*

2-chloro-2-deoxy-D-glucose. Carry out the test as described in *High performance liquid chromatography* **(5.2.17.4)**. Use a high performance liquid chromatograph equipped with a pulsed amperometric detector and a 250 mm (L) x 4 mm (internal diameter) column, 10 µm packing strongly alkaline anionic resin; 0.5 mL/min of flow rate.

Mobile phase: prepare 1000 mL of a 0.2 M sodium hydroxide solution, filter and degas with helium.

System suitability: weigh appropriate amounts of fludeoxyglucose CRS and 2chloro-2-deoxy-D-glucose CRS and dissolve in the mobile phase to obtain 1 mg/mL and 0.1 mg/mL solutions, respectively.

Sample solution: fludeoxyglucose (18 F) injection to be analyzed.

Standard solution: 0.1 mg/mL 2-chloro-2-deoxy-D-glucose CRS solution.
System suitability: separately inject the Standard solution and the System suitability solution and record the chromatogram according to the Procedure. The resolution between fludeoxyglucose and 2-chloro-2-deoxy-D-glucose must be at least 1.5, and the relative standard deviation for repeated injections must be at most 5 %.

Procedure: Separately inject equal volumes (approximately 100 µL) of the *Standard solution* and the *Sample solution*. Record the chromatograms and measure the area of the main peaks.

Calculate the amount in mg of 2-chloro-2-deoxy-D-glucose, in each mL of the *Sample solution* (C_a) using the following formula:

$$C_a = C_p \, (r_a/r_p)$$

where:

C_p is the concentration of 2-chloro-2-deoxy-D-glucose in the *Standard solution (mg/ml)*;
r_a and r_p are the areas of peaks of 2-chloro-2-deoxy-D-glucose, from the *Sample solution* and the *Standard solution*, respectively.

The amount of 2-chloro-2-deoxy-D-glucose in the *Sample solution* (C_a) should be not more than 1 mg per dose.

Residual solvents. Carry out the test as described in Gas chromatography **(5.2.17.5)**. The gas chromatograph is equipped with a flame ionization detector, split mode injection system (1:20 rate) and a 0.25 mm (internal diameter) x 30 m (L) fused-silica column coated with a 0.50 µm film thickness cross-linked polyethylene glycol (MW around 15000). Helium is the carrier gas with 2 mL/min of flow rate. The method program is the following: initially the temperature is maintained at 40 ºC for one minute. Then increase 40 ºC/min until reaching 100 ºC and keep for one minute. The injector and detector temperature must be maintained at 250 ºC and 300 ºC, respectively.

Sample solution: fludeoxyglucose (18 F) injection to be analyzed.

Standard solution: an aqueous solution containing 0.01 % acetonitrile (w/v), 0.1 % ethanol (w/v) and 0.1 % ether (w/v).

System suitability: inject approximately 1 µL of the *Standard solution* in triplicate and record the peak response. The resolution between any two components must be at least 1.0 and the relative standard deviation for the areas of the injection replicates must be at most 5 %.

Procedure: separately inject equal volumes (approximately 1 µL) of the *Sample solution* and the *Standard solution*. Record the chromatograms and measure the peak areas

Calculate the concentration of residual solvent in the *Sample solution* as follows:

$$C_a = C_p\ (r_a/r_p)$$

where:

C_a = percentage of solvent in the *Sample solution* (%);
C_p = percentage of solvent in the *Standard solution* (%);
r_a/r_p = peak area of *Sample solution*/peak area of the *Standard solution*.

maximum, 0.04% of acetonitrile, 0.5% of ethanol and 0.5% of ether.

Radionuclidic purity. Carry out the test as describing in *Radiopharmaceuticals* **(9).** Determine using a suitable calibrated gamma-ray spectrometer. In the resultant gamma spectrum, at least 99.5 % must correspond to 0.511 MeV main peak, 1.022 MeV sum peak or Compton-scattering peaks of 18 F.

BIOLOGICAL SAFETY TESTS

Sterility (5.5.3.2.1). Meets the requirements. The product can be used before the conclusion of sterility test.

Bacterial endotoxins (5.5.2.2). It must contain less than 175 UE/V, where *V* is the maximum recommended dose, in mL, at the expiration date or time.

RADIOACTIVITY

Carry out the test as described in *Radiopharmaceuticals* **(8.3)**. Use a suitable and calibrated counting instrument, determine the radioactivity in Bq (Ci) or its multiples and sub-multiples, per volume unit.

PACKAGING AND STORAGE

Carry out as described in *Radiopharmaceuticals* **(8.3)**. Keep in a perfectly closed container, in a radiation protection shield.

LABELING

Following the current legislation.

USE

Diagnostic.

SODIUM MEDRONATE (99m Tc), INJECTION

Technetii (^{99m}Tc) medronati injectio

[99m Tc]$(CH_6O_8P_2)_n$
sodium medronate (99m Tc); 09794
MDP-^{99m}Tc; sodium methylene diphosphonate (99m Tc)
[*121524-79-6*]

It contains not less than 90 percent and not more than 110 percent sodium medronate (99m Tc), expressed in MBq/mL (mCi/mL), at the date and time stated on the label.

DESCRIPTION

Technetium-99m sodium medronate injection is a sterile, clear aqueous solution. It is a complex formed by sodium medronate and technetium-99m, from the sodium pertechnetate (99m Tc) injection solution, in presence of a reducing agent. Other chemicals forms of radioactivity do not exceed 10 percent of the total radioactivity. It may contain preservatives, stabilizers, antimicrobial agents and suitable buffer solutions.

IDENTIFICATION

A. The product must meet the requirements of the Radionuclidic Identification test and of Radionuclidic Purity from the monograph Sodium pertechnetate (99m Tc), injection.

B. Examine the chromatogram obtained in the radiochemical purity test. The activity distribution contributes to the identification of the preparation.

PURITY TESTS

pH (5.2.19). 4.0 to 8.0.

Radiochemical purity Carry out the test as described in *Paper chromatography* **(5.2.17.2)**, ascending type.

Sample solution: sodium medronate (99m Tc) injection to be analyzed.

A. *Stationary phase*: use a chromatographic paper strip.
Mobile phase: sodium chloride solution 0.9% (w/v).
Procedure: Place 2 to 5 µL of a dilution of the *Sample solution* on the paper strip suitable to the sensitivity of the detection equipment. Develop the chromatogram immediately and over a suitable period to allow the specimens to separate and allow it to air-dry. Determine the distribution of radioactivity using an appropriate detector. Free pertechnetate and the sodium medronate (99m Tc) migrate with the solvent front (Rf 0.9-1.0). Technetium-99m in colloidal form is located at origin (Rf 0.0-0.1).

B. *Stationary phase*: use a chromatographic paper strip.

Mobile phase: acetone.
Procedure: place 2 to 5 µL of a dilution of the *Sample solution* on the paper strip suitable to the sensitivity of the detection equipment. Develop the chromatogram immediately and over a suitable period to allow the specimens to separate and allow it to air-dry. Determine the distribution of radioactivity using an appropriate detector. Free pertechnetate migrates with the solvent front (Rf 0.9-1.0). Sodium medronate (99m Tc) and technetium-99m in colloidal form are located at origin (Rf 0.0-0.1).

The percentage of radioactivity corresponding to the sum of percentages of radioactivity due to technetium in colloidal form, determined in the test A and free technetium-99m, determined in the test B, must not exceed 10.0%.

BIOLOGICAL SAFETY TESTS

Sterility (5.5.3.2.1). Meets the requirements.

Bacterial endotoxins (5.5.2.2). It must contain less than 175 UE/V, where *V* is the maximum recommended dose, in mL, at the expiration date or time.

Biological distribution. Inject intravenously in a volume not exceeding 0.2 mL, equivalent to, at most, 0.05 mg of sodium medronate, on the caudal or saphenous vein of three rats (150-250 g). Measure the syringe activity before and after administering. Sacrifice the animals one hour after the injection and carefully remove a femur, the liver, and the kidneys. Extirpate the tail if the vein was used for injection. Determine the percentage of radioactivity in each organ according to the expression:

$$(A/B)\times 100$$

where:

A is the organ radioactivity and B is the total radioactivity, equivalent to the difference between the two measures from the syringe, less the tail activity.

A minimum of 1% of the injected radioactivity must be found on the femur and a maximum of 5% on the liver or kidneys in at least two of the three animals.

RADIOACTIVITY

Carry out of the test as described in *Radiopharmaceuticals* **(8.3)**. Using an suitable and calibrated counting instrument, determine the radioactivity in Bq (Ci) or its multiples and sub-multiples, per volume unit.

PACKAGING AND STORAGE

Carry out as described in Radiopharmaceuticals **(8.3)**. Keep in a perfectly closed container, in a radiation protection shield.

LABELING

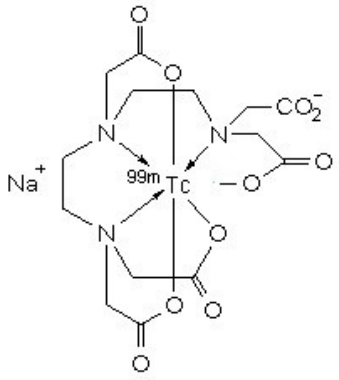
Following the current legislation.

USE

Diagnostic.

SODIUM PENTETATE (99m Tc), Injection

Technetii (^{99m}Tc) pentetatis injectio



[^{99m}Tc]$C_{14}H_{18}N_3NaO_{10}$; 510.2 g/mol
sodium pentetate (99m Tc); 09748
[*N, N*-bis{2-[bis(carboxylmethyl)amino]ethyl}glycinate(5-)]sodium [99mTc]technetate(1-);
DTPA-99mTc
[*65454-61-7*]

It contains not less than 90 percent and not more than 110 percent of sodium pentetate (99m Tc), expressed in MBq/mL (mCi/mL), at the date and time stated on the label.

DESCRIPTION

Technetium-99m sodium pentetate injection is a sterile, clear aqueous solution. It is a complex formed by sodium pentetate and technetium-99m, from the sodium pertechnetate (99m Tc) injection solution, in presence of a reducing agent. Other chemicals forms of radioactivity do not exceed 10 percent of the total radioactivity. It may contain preservatives, stabilizers, antimicrobial agents and suitable buffer solutions.

IDENTIFICATION

A. The product must meet the requirements of the Radionuclidic Identification test and of Radionuclidic Purity from the monograph *Sodium pertechnetate (99m Tc), injection.*

B. Examine the chromatogram obtained in the radiochemical purity test. The activity distribution contributes to the identification of the preparation.

PURITY TESTS

pH (5.2.19). 3.8 to 7.5.

Radiochemical purity. Carry out the test as described in *Paper chromatography* **(5.2.17.2)**, ascending type.

Sample solution: sodium pentetate (99m Tc) injection to be analyzed.
A. *Stationary phase*: use a chromatographic paper strip.
Mobile phase: sodium chloride solution at 0.9% (w/v).
Procedure: place 2 to 5 µL of a dilution of the *Sample solution*, on the paper strip, suitable to the sensitivity of the detection equipment. Develop the chromatogram immediately and over a suitable period to allow the specimens to separate and allow it to air-dry. Determine the distribution of activity using an appropriate detector. Free pertechnetate and the sodium pentetate (99m Tc) migrate with the solvent front (Rf 0.9-1.0). Technetium-99m in colloidal form located at origin (Rf 0.0-0.1).

B. *Stationary phase*: use a chromatographic paper strip.
Mobile phase: acetone.
Procedure: place 2 to 5 µL of a dilution of the *Sample solution*, on the paper strip, suitable to the sensitivity of the detection equipment. Develop the chromatogram immediately and over a suitable period to allow the specimens to separate and allow it to air-dry. Determine the distribution of activity using an appropriate detector. Free pertechnetate migrates with the solvent front (Rf 0.9-1.0). Sodium pentetate (99m Tc) and technetium-99m in colloidal form are located at origin (Rf 0.0-0.1).

The percentage of radioactivity corresponding to the sum of percentages of radioactivity due to technetium in colloidal form, determined in the test A and free technetium-99m, determined in the test B, must not exceed 10.0 %.

BIOLOGICAL SAFETY TESTS

Sterility (5.5.3.2.1). Meets the requirements

Bacterial endotoxins (5.5.2.2). It must contain less than 175 UE/V, where V is the maximum recommended dose, in mL, at the expiration date or time.

Biological distribution. Inject intravenously in a volume not exceeding 0.2 mL of sodium pentetate (99m Tc) injection on the caudal or saphenous vein of three rats (150-250 g). Measure the syringe activity before and after administering. Extirpate the tail, if the caudal vein was used for injection. Determine the percentage of radioactivity in each organ according to the expression:

$$(A/B)\times 100$$

where:

A is the organ radioactivity and B is the total radioactivity, equivalent to the difference between the two measures from the syringe, less the tail activity.

Two hours after the injection, the sum of percentages of radioactivity found in the urine and bladder must be higher than 85% of the injected radioactivity and less than 1% of the radioactivity injected must be found in the liver of at minimum two of the three animals.

RADIOACTIVITY

Carry out the test as described in Radiopharmaceuticals (**8.3**). Using a suitable and calibrated counting instrument, determine the radioactivity in Bq (Ci) or its multiples and sub-multiples, per volume unit.

PACKAGING AND STORAGE

Carry out as described in Radiopharmaceuticals **(8.3)**. Keep in a perfectly closed container, in a radiation protection shield.

LABELING

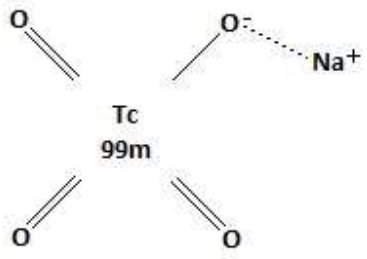
Following the current legislation.

USE

Diagnostic.

SODIUM PERTECHNETATE (99m Tc), INJECTION

Technetii (^{99m}Tc) injectio



$Na[^{99m}Tc]O_4$; 185.89 g/mol
sodium pertechnetate (99m Tc); 09750
pertechnetic acid ($H^{99m}TcO_4$), sodium salt
[*23288-60-0*]

It contains not less than 90 percent and not more than 110 percent of sodium pertechnetate (99m Tc) expressed in MBq/mL (mCi/mL), at the date and time stated on the label.

DESCRIPTION

Sterile and colorless solution of sodium pertechnetate (99m Tc), prepared from isotonic sodium chloride solution Sodium pertechnetate (99m Tc) injection is a sterile, clear aqueous solution that is prepared from sodium chloride solution isotonic. Sodium pertechnetate (99m Tc) injection is produced by chemical separation of the radioactive decay of parent radionuclide molybdenum-99.
At least 95 percent of the total technetium-99m (99m Tc) radioactivity should be present as pertechnetate ion. Technetium-99m is a gamma emitting radionuclide, with a halt-life of 6,007 hours, formed by the decay of molybdenum-99 (99 Mo). Molybdenum-99 is a radioactive isotope of molybdenum and may be formed as a product of uranium fission or by the neutron bombardment of molybdenum-98 (98 Mo).

IDENTIFICATION

The gamma spectrum, obtained with a properly calibrated gamma spectrometry system, must correspond to the spectrum of technetium-99m concerning its energies and intensities, as indicated under *Radiopharmaceuticals* **(8.3)**. The main gamma photon of 99m Tc has an energy of 140 keV.

PURITY TESTS

pH (5.2.19). 4.0 to 8.0.

Aluminum.

Note: *To be determined if, in obtaining the sodium pertechnetate (99m Tc) solution, separation is accomplished by an alumina column in the preparation of the Injection.*

Sample solution: dilute 1 mL of the sodium pertechnetate (99m Tc) injection to 2.5 mL, with water.
Reference solution: prepare at the same time as the *Sample solution* and use 2 mL of the standard aluminum solution (2 ppm Al).

Aluminum standard solution: dissolve in water 35.17 mg of aluminum potassium sulfate dodecahydrate (CRS) accurately weighed, dilute to 1000 mL. Each mL of this solution contains 2 µg of Al.

Procedure: in a test tube of about 12 mm in internal diameter, mix 1 mL of 0.5 *M* acetate buffer solution, pH 4.6 and 2 mL of the *Sample solution*. Add 50 µL of a 10 g per liter chrome azurol solution. After three minutes, the color of the solution is not more intense than that of an aluminum standard. The concentration of aluminum ion in the Injection is not greater than 5 ppm Al.

Methyl ethyl ketone.
Note: *determine if the separation is accomplished by liquid-liquid extraction in the preparation of the injection*
Procedure: place 1 mL of the injectable solution to an adequate container and dilute with water to 20 mL. Add 2 mL of 1 *M* sodium hydroxide, mix, then add 2 mL of 0.1 *M* iodine, dropwise, and again mix. At the same time, prepare a standard by placing 1 mL of a methyl ethyl ketone solution (1 in 1000) to a similar container and diluting with water to 20 mL. Add 2 mL of 1 *M* sodium hydroxide, mix, then add 2 mL of 0.1 *M* iodine, dropwise, and again mix. After two minutes, the turbidity of the *Sample solution* does not exceed that of the standard (0.1%).

Radionuclidic purity.
Preliminary assay obtain an approximate estimate, before using the sodium pertechnetate (99m Tc) injection, using a volume of technetium-99m solution that has approximately 370 MBq (10 mCi) and determine its activity with a properly calibrated activity meter using the technetium-99m scale, as indicated in *Radiopharmaceuticals* **(9)**. Register the activity. Measure the activity of molybdenum-99 in the same *Sample solution*, changing the activity meter scale to molybdenum-99 and placing the *Sample solution* inside the 6 mm lead shielding, necessary for such determination. The maximum activity of molybdenum-99 is not more than 0.15 kBq per MBq (0.15 µCi per mCi) of technetium-99m, from the previously determined measure.

Purity assay in the decayed test solution: keep a sample of the sodium pertechnetate (99m Tc) injection to be analyzed, for a sufficient interval (three to five days) so that the radioactivity of technetium-99m decreases and enables the detection of radionuclidic impurities. All activity measurements must refer to the date and time of administration. Obtain the gamma radiation spectrum of the test solution using a high resolution gamma spectrometry system.

For the injectable solution prepared from technetium-99m derived of the precursor molybdenum-99 as the result of neutron bombardment of stable molybdenum, proceed to the tests described below:

MOLYBDENUM-99: the presence of molybdenum-99 in the injectable solution is evident by its characteristic gamma ray spectrum. The most prominent photopeaks of this radionuclide have energies

of 0.181; 0.740 and 0.780 MeV. The activity of molybdenum-99 is no grater than 0.15 kBq per MBq (0.15μCi per mCi) of technetium-99m, per administered dose, at the time of administration.

OTHER GAMMA RAY-EMITTING RADIONUCLIDIC IMPURITIES: the total activity of other emitting radionuclidic impurities does not exceed 0.5 kBq per MBq (0.5 μCi per mCi) of technetium-99m, or 92 kBq (2.5 μCi) per administered dose at the time of administration.

For the injectable solution prepared from technetium-99m derived of the precursor molybdenum-99 obtained as the result of fission of uranium, proceed to the tests described below:

MOLYBDENUM-99: the injectable solution must meet the requirements established for injection prepared by irradiation of stable molybdenum with neutrons (as previously described).

IODINE-131: the most prominent photopeak of this radionuclide has 0.364 MeV of energy. The maximum activity of iodine-131 is not more than 0.05 kBq per MBq (0.05 μCi per mCi) of technetium-99m, at the time of administration.

RUTHENIUM-103: the most prominent photopeak of this radionuclide has 0.497 MeV of energy. The maximum activity of ruthenium-103 is not more than 0.05 kBq per MBq (0.05 μCi per mCi) of technetium-99m, in the moment of administration.

STRONTIUM-89: determine the presence of strontium-89 in the injection by a suitable and calibrated counting instrument for detecting corpuscular radiation. Strontium-89 disintegrates by beta emission, with maximum energy of 1.463 MeV. The maximum activity of strontium-89 is not more than 0.0006 kBq per MBq (0.0006 μCi per mCi) of technetium-99m, at the time of administration.

STRONTIUM-90: determine the presence of strontium-90 in the injection by using an counting system adequate for detecting corpuscular radiation. Strontium-90 disintegrates by beta emission, with maximum energy of 0.546 MeV. The maximum activity of strontium-90 is not more 0.00006 kBq per MBq (0.00006 μCi per mCi) of technetium-99m, at the time of administration.

OTHER RADIONUCLIDIC IMPURITIES: the activities of other radionuclidic impurities that emit gamma and beta rays must correspond to a maximum of 0.01% at the time of administration. The total alpha activity is not more than 0.001 Bq per 1 MBq (or 0.001 μCi per 1 mCi) of technetium-99m, at the time of administration.

Radiochemical purity. Carry out the test as described in *Paper chromatography* **(5.2.17.2)**, ascending type.

Sample solution: dilute the sodium pertechnetate (99m Tc) injection with water to obtain an adequate radioactive concentration to the detection system.
Stationary phase: use a chromatographic paper strip.
Mobile phase: methyl alcohol and water (85:15).
Procedure: Place on the paper strip 2 to 5 μL of the *Sample solution*. Develop the chromatogram immediately and for a sufficient period of time that enables the separation of the specimens and allow it to air-dry. Determine the distribution of activity using an appropriate instrument. The value of Rf corresponding to pertechnetate ion is between 0.9 and 1.0. The radioactivity of the pertechnetate ion is not less than 95% of the total radioactivity in the test specimen.

BIOLOGICAL SAFETY TESTS

Sterility (5.5.3.2.1).
Meets the requirements

Bacterial endotoxins (5.5.2.2). It must contain less than 175 UE/V, where *V* is the maximum recommended dose in mL, at the expiration date or time.

RADIOACTIVITY

Carry out the test as described in Radiopharmaceuticals (**8.3**). Use a suitable and calibrated counting instrument, determine the radioactivity in Bq (Ci) or its multiples and sub-multiples, per volume unit.

PACKAGING AND STORAGE

Carry out as described in Radiopharmaceuticals (**8.3**). Keep in a perfectly closed container, in a radiation protection shield.

LABELING

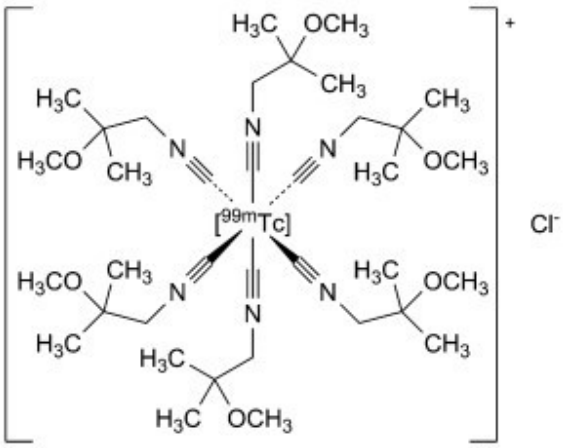
Following the current legislation.

USE

Diagnostic.

SESTAMIBI (99m Tc), INJECTION

Technetii (^{99m}Tc) sestamibi injectio



[99mTc]$C_{36}H_{66}N_6O_6$; 775.41
Technetium (99m) Sestamibi; 08338
(*OC*-6-11)-hexakis[1-(isocyane-κ*C*)-2-methoxy-2-methylpropane] [99mTc]technetium(I) chloride;
MIBI-^{99m}Tc
[*109581-73-9*]

It contains not less than 90 percent and not more than 110 percent of labeled amount of the radioactivity of sestamibi (99m Tc), at the date and time stated on the label.

DESCRIPTION

Sestamibi (99m Tc) injection is a sterile, clear solution of tetrakis(2-methoxy-2-methylpropyl-1-isocyanide) copper (I) tetrafluoroborate that is labeled with technetium-99m from sodium pertechnetate (99m Tc) injection, in the presence of a reducing agent and a weak chelating agent. Other chemicals forms of radioactivity do not exceed 10% of the total radioactivity. It may contain preservatives, stabilizers, antimicrobial agents and suitable buffer solutions.

IDENTIFICATION

A. The product must comply with the requirements from the Radionuclidic identification test and of Radionuclidic purity from the monograph *Sodium pertechnetate (99m Tc), injection*.

B. Examine the chromatogram obtained in the radiochemical purity test. The radioactivity distribution contributes to the identification of the preparation.

PURITY TESTS

pH (5.2.19). 5.0 to 6.0.

Radiochemical purity.

A. Carry out the test as described in *Thin-layer chromatography* **(5.2.17.1)**.

Sample solution: sestamibi (99m Tc) injection to be analyzed.
Stationary phase: reverse phase chromatographic plate (silica chemically linked to octadecylsilane group) with adequate dimensions.
Mobile phase: solution of acetonitrile : methanol: ammonium acetate 3.85%: tetrahydrofuran (4:3:2:1).
Procedure: Place on the chromatographic plate 2 to 5 µL of a dilution of the *Sample solution*, suitable for the sensitivity of the detection equipment. Develop the chromatogram immediately for a sufficient period of time that allows separating the specimens and allow it to air-dry. Determine the distribution of activity using an appropriate detector.

The Rf value corresponding to sestamibi (99m Tc) and to the impurity (*OC*-6-22)-pentakis[1-(isocyaneκ*C*)-2-methoxy-2-methylpropane][1-(isocyane-κ*C*)-2-methylprop-1-ene][^{99m}Tc]technetium(1+), also known as pentamibi (99m Tc), is between 0.3 and 0.6. Pertechnetate (99m Tc) ion is located at about the Rf 0.8 and 1.0 and technetium-99m in colloidal form is located at about Rf 0.0 and 0.1 minimum 90% of the total activity must be between Rf 0.3 and 0.6. The maximum percentage of radioactivity corresponding to the sum of percentages of radioactivity of the impurities free pertechnetate (99m Tc) ion and technetium-99m in colloidal form must be 10%.

B. Carry out the test as described in *High performance liquid chromatography* **(5.2.17.4)**. Use a liquid chromatograph equipped with radioactivity detector; analytical column with 300 mm of length and 3.9 mm of diameter, packaged with silica chemically linked to octadecylsilane group (10 µm); Mobile phase flow of approximately 2 mL per minute. If the peak impurity pentamibi (99m Tc) is present, its relative retention in relation to the peak sestamibi (99m Tc) is from 1.3 to 1.5.

Sample solution: sestamibi (99m Tc) injection to be analyzed.

Mobile phase: prepare a filtered and degassed mixture of methanol, ammonium sulfate solution 0.05 *M* and acetonitrile (45:35:20).

Procedure: inject approximately 5 µL (9.375 MBq or 250 µCi) of sestamibi (99m Tc) injection in the liquid chromatograph and adjust the integrator/recording device so that the peak is between 25% and 100% of the fullscale. separately, injectequal volumes (approximately 5 µL, 9.375 MBq or 250 µCi) of the *Sample solution* in the chromatograph, record the chromatograms, and measure the area percentage for all the peaks presented. The retention time of sestamibi (99m Tc) is about 5 to 10 minutes. the retention time of the impurity pentamibi (99m Tc) is about 6 to 13 minutes. Correct for the presence of technetium-99m in colloidal form, which is not determined by this method, using the following equation:

$$F = (100\% - P) / 100$$

where:

F is the correction factor and *P* is the percentage of technetium-99m in colloidal form acquired by this method **A**. Obtain the corrected area percentage by multiplying F by the percentage area of the peaks presented in the chromatogram.

A mean of not less than 90% (corrected area percentage) of the total radioactivity is represented by sestamibi (99m Tc), and a mean of not more than 5% (corrected area percentage) of the total radioactivity is present as pentamibi (99m Tc).

BIOLOGICAL SAFETY TESTS

Sterility (5.5.3.2.1). Meets the requirements

Bacterial endotoxins (5.5.2.2). It must contain less than 175 UE/V, where *V* is the maximum recommended dose in mL, at the expiration date or time.

RADIOACTIVITY

Carry out the test as described in *Radiopharmaceuticals* **(8.3**). Using an suitable and calibrated counting instrument, determine the radioactivity in Bq (Ci) or its multiples and sub-multiples, per volume unit.

PACKAGING AND STORAGE

Carry out as described as in *Radiopharmaceuticals* **(8.3)**. Keep in a perfectly closed container, in a radiation protection shield.

LABELING

Following the current legislation.

USE

Diagnostic.