THE INTERNATIONAL PHARMACOPOEIA

RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

TECHNETIUM\textsuperscript{99m} EXAMETAZI IMI MULTIPLEX INJECTION
TECHNETIUM\textsuperscript{99m} EXAMETAZIME COMPLEX INJECTION
(March 2014)

REVISED DRAFT FOR COMMENT

Should you have any comments on the attached text, please send these to:
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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.

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THE INTERNATIONAL PHARMACOPOEIA
RADIO PHARMACEUTICALS: SPECIFIC MONOGRAPH
TECHNETII (99mTc) EXAMETAZIMI MULTIPLEX INJECTIO
TECHNETIUM (99mTc) EXAMETAZIME COMPLEX INJECTION

Monographs: Radiopharmaceuticals: Specific monographs: Technetii (99mTc) exametazimi multiplex injectio - Technetium (99mTc) exametazime complex injection

Latin. Technetii (99mTc) exametazimi multiplex injection.

English. Technetium (99mTc) exametazime complex injection.

Structural formula

\[
\text{C}_{13}\text{H}_{25}\text{N}_{4}\text{O}_{3}^{\text{99mTc}}
\]

Relative molecular mass. 384.269

Chemical name. Racemic mixture of (3RS,9RS)-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime complex with (99mTc) technetium.

Other names. (99mTc)-D,L-Hexamethylpropyleneamine oxime complex injection; (99mTc)-D,L-HMPAO injection.

Description. Technetium (99mTc) exametazime complex injection is a clear, colourless aqueous solution. Technetium-99m has a half-life of 6.01 hours.

Category. Diagnostic.

Storage. Technetium (99mTc) exametazime complex injection should be kept at a temperature between 2 °C to 8 °C.
Technetium ($^{99m}$Tc) exametazime complex injection should be used within 30 minutes of reconstitution of the unlabelled kit with Technetium-99m, unless the preparation has been stabilized with cobalt chloride solution or methylene blue solution or any other stabilizer.

**Labelling.** The label complies with the General monograph, the monograph of Radiopharmaceuticals. The label includes the name stabilizer if added.

**Manufacture.** Technetium ($^{99m}$Tc) exametazime injection is prepared aseptically from sterile starting materials such as a sterile kit containing a mixture of (3RS, 9RS)-4, 8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime and stannous salt with Sodium pertechnetate ($^{99m}$Tc) injection (Fission) or Sodium Pertechnetate ($^{99m}$Tc) injection (Non-fission). The injection may have the pH adjusted and may contain stabilizing agents. 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 millilitre.

**Requirements**

Complies with the monograph for Parenteral Preparations and with that for Radiopharmaceuticals.

**Definition.** Technetium ($^{99m}$Tc) exametazime injection is a sterile lipophilic solution of racemic mixture of (3RS, 9RS)-4, 8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime (exametazime) complexes with sodium pertechnetate ($^{99m}$Tc) injection (fission or non-fission) in presence of stannous salt. The injection is suitable for intravenous administration and contains sufficient sodium chloride to make the solution isotonic with blood. The content of technetium-99m is not less than 90% and not more than 110% of the content of technetium-99m. Not less than 80% of the total technetium-99m radioactivity is present as lipophilic ($^{99m}$Tc) exametazime complex and its meso isomer.

**Identity tests**

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

A. Record the gamma-ray spectrum using a suitable instrument with a sample of technetium-99m, suitably diluted if needed. The spectrum is concordant with the reference spectrum of a specimen of technetium-99m in that it exhibits a major peak of 142 keV.

Standardized technetium-99m solutions are available from competent laboratories recognized by the relevant national or regional authority.

B. The half-life determined using a suitable detector system is between 5.72 and 6.32 hours.

C. Examine the chromatograms obtained in the test of Impurity A under Radiochemical purity. The principal peak in the chromatogram obtained with the test solution is similar in retention time to the peak due to lipophilic technetium-99m exametazime in the chromatogram obtained with the reference solution.
**pH value.** Carry out the test as described under 1.13 **Determination of pH** or R1.5 under the monograph for Radiopharmaceuticals. The pH of the injection is between 5.0 and 10.0.

**Sterility.** The injection complies with 3.2 Test for sterility, modified as described in the monograph for Radiopharmaceuticals. Test for sterility will be initiated on the day of manufacture. The injection 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, modified as described in the monograph for Radiopharmaceuticals. The injection contains not more than 175/µl of endotoxins per millilitre.

**Radionuclidic purity.** Complies with the tests of radionuclidic purity under the monographs of Sodium pertechnetate (99mTc) injection (Fission) or Sodium Pertechnetate (99mTc) injection (Non-fission) used for the preparation of Technetium (99mTc) exametazime injection. Not less than 99.9% of the total radioactivity is due to technetium-99m.

**Radiochemical purity**

**Impurity C.** Carry out the test described under 1.14.1 Thin-layer chromatography for impurity C use TLC silica gel plate R, a glass fiber plate and 9 g/L solution of sodium chloride as a mobile phase. Apply to the plate about 5 µl of the injection to be examined and develop immediately for a distance over 2/3 of the plate. Allow the plate to dry in air and determine the radioactivity distribution using a suitable detector. Impurity C has Rf value of 0.8 to 1.0; lipophilic technetium-99m exametazime and impurities A, B, D and E do not migrate. The maximum limit of impurity C is 10% of the total radioactivity.

**Total of lipophilic technetium-99m exametazime and impurity A.** Carry out the test under 1.14.1 Thin-layer chromatography. Use TLC silica gel plate R, a glass fibre plate and methyl ethyl ketone as a mobile phase. Apply to the plate about 5 µl of the injection to be examined and develop immediately for a distance over 2/3 of the plate. Allow the plate to dry in air and determine the radioactivity distribution using a suitable detector. The lipophilic technetium-99m exametazime, impurities A and C have Rf value of 0.8 to 1.0; for impurities B, D and E do not migrate.

Calculate the percentage of radioactivity due to impurities B, D and E from test C and the percentage of the radioactivity due to impurity C from test B. Calculate the total percentage of lipophilic technetium-99m exametazime and impurity A from the expression: 100 - A - B.

Not less than 80% of the total technetium-99m radioactivity is present as lipophilic technetium-99m exametazime and impurity A.

**Impurity A.** Carry out 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 particles of silica gel, the surface of which has been modified with chemically-bonded octadecylsilyl groups (5 µm). As a mobile phase use a mixture of 33 volumes of acetonitrile R and 67 volumes of 0.1 M phosphate buffer solution R pH 3.0 to use as mobile phase. The flow rate is 1.5 mL/min, the detector is radioactivity detector with loop injector and the run time is 20 min. Prepare the reference solution by dissolving the contents of a vial of meso-rich exametazime CRS in 0.5 ml of a 9 g/L solution of sodium chloride and transfer to a
lead-shielded, nitrogen-filled vial. Add 6 µL of a freshly prepared 1 g/L solution of stannous chloride R in 0.05 M hydrochloric acid and 2.5 mL of sodium pertechnetate (99mTc) injection (fission or non-fission) containing 370–740 MBq. Mix carefully and use within 30 min of preparation. The relative retention with reference to lipophilic technetium-99m exametazime to impurity A is about 1.2.

The produced chromatogram is similar to the chromatogram provided with meso-rich exametazime CRS. The resolution is minimum of 2 between the peaks due to lipophilic technetium-99m exametazime and to impurity A. Impurity A should not more than 5% of the radioactivity due to lipophilic technetium-99m exametazime and impurity A.

**Tin estimation.** Carry out the test as described under R2.1.4 Tin estimation by UV absorption, using 1.0 ml of a test solution prepared by diluting 1.5 ml of the injection to be examined to 25.0 ml with hydrochloric acid (103 g/L) VS and mixing thoroughly. Prepare the reference solution by dissolving 0.115 g of stannous chloride R using a solution in hydrochloric acid R (103 g/L HCl) and dilute to 1000.0 mL using the same acid. To the test solution and to 1 mL of each of the reference solutions add 0.05 mL of thioglycollic acid R, 0.1 mL of dithiol reagent R, 0.4 mL of a 20 g/L solution of sodium laurilsulfate R, 3 mL of 21g/L solution of hydrochloric acid R. Mix and measure the absorbance of each solution at 540 nm using 21g/L solution of hydrochloric acid as a compensation liquid. The absorbance of the test solution is not greater than that of the reference solution; not more than 0.6 µg of Sn per ml.

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

**Impurities**

A. Meso isomer of lipophilic technetium-99m exametazime,
B. Technetium-99m in colloidal form,
C. [99mTc]pertechnetate ion,
D. Non lipophilic technetium-99m exametazime complex,
E. Meso isomer of non-lipophilic technetium-99m exametazime complex.

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