THE INTERNATIONAL PHARMACOPOEIA

RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

TECHNETIUM (99mTc) EXAMETAZIMI MULTIPLEX INJECTIO

TECHNETIUM (99mTc) EXAMETAZIME COMPLEX INJECTION

(June 2013)

DRAFT FOR REVISION

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### SCHEDULE FOR THE ADOPTION PROCESS OF DOCUMENT QAS/13.548

**THE INTERNATIONAL PHARMACOPOEIA**

**RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH**

*TECHNETIUM (\(^{99m}\)Tc) EXAMETAZIME MULTIPLEX INJECTION*

*TECHNETIUM (\(^{99m}\)Tc) EXAMETAZIME COMPLEX INJECTION*

<table>
<thead>
<tr>
<th>Event Description</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>IAEA consultation</td>
<td>3-7 December 2012</td>
</tr>
<tr>
<td>IAEA consultation</td>
<td>6-10 May 2013</td>
</tr>
<tr>
<td>Draft monograph received from IAEA in track-change mode according to format/template described in QAS/13.544</td>
<td>June 2013</td>
</tr>
<tr>
<td>Discussion at informal consultation on new medicines, quality control and laboratory standards</td>
<td>12-14 June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA by WHO Secretariat</td>
<td>June 2013</td>
</tr>
<tr>
<td>Circulation for comments to IAEA and WHO Panel of Experts</td>
<td>June 2013</td>
</tr>
<tr>
<td>Feedback to IAEA, as appropriate</td>
<td>August-September 2013</td>
</tr>
<tr>
<td>Discussion during WHO Expert Committee on Specifications for Pharmaceutical Preparations for discussion</td>
<td>October 2013</td>
</tr>
<tr>
<td>Further follow-up action as required</td>
<td></td>
</tr>
</tbody>
</table>
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RADIOPHARMACEUTICALS: SPECIFIC MONOGRAPH

TECHNETII (99M\textsubscript{Tc}) EXAMETAZIMI MULTIPLEX INJECTIO

TECHNETIUM (99M\textsubscript{Tc}) EXAMETAZIME COMPLEX INJECTION

Monographs: Radiopharmaceuticals: Specific monographs: Technetii (99m\textsubscript{Tc}) exametazimi multiplex injectio - Technetium (99m\textsubscript{Tc}) exametazime complex injection

Latin. Technetii (99m\textsubscript{Tc}) exametazimi multiplex injection.

English. Technetium (99m\textsubscript{Tc}) exametazime complex injection.

Structural formula

![Structural formula image]

Empirical formula. \(C_{13}H_{25}N_4O_3\cdot99m\textsubscript{Tc}\)

Relative molecular mass. 384.269

Chemical name: Racemic mixture of (3\textsubscript{RS},9\textsubscript{RS})-4,8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime complex with (99m\textsubscript{Tc}) technetium.

Other names. (99m\textsubscript{Tc})-\textit{D,L}-Hexamethypropyleneamine oxime complex injection; (99m\textsubscript{Tc})-\textit{D,L}-HMPAO injection.

Description: Technetium (99m\textsubscript{Tc}) exametazime complex injection is a clear, colourless aqueous solution.

Technetium-99m has a half-life of 6.02 hours.

Category: Diagnostic.
Storage: Technetium ($^{99m}\text{Tc}$) exametazime complex injection should be kept at a temperature between 2°C to 8°C.

Technetium ($^{99m}\text{Tc}$) 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 either cobalt chloride solution or methylene blue solution.

Labelling: State the date and the time of calibration; the amount of $^{99m}\text{Tc}$ as labelled exametazime expressed as total MBq and the concentration expressed as MBq/ml; the expiration date; and the statement “Caution- Radioactive material”. The labelling indicates that in making dosage calculations, correction is to be made for radioactive decay, and indicates that the half-life of $^{99m}\text{Tc}$ is 6.02 hours. The label states that upon constitution with Sodium Pertechnetate $^{99m}\text{Tc}$ injection, beyond use time is 30 minutes for the unstabilized injection, and between 4 hours and 6 hours for the stabilized injections.

Manufacture: Technetium-99m is a radioactive nuclide formed by the radioactive decay of molybdenum-99. Molybdenum-99 is a radioactive isotope of molybdenum and may be produced by neutron irradiation of natural molybdenum or of molybdenum enriched in molybdenum-98 or it may be produced by uranium fission.

Technetium ($^{99m}\text{Tc}$) 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 ($^{99m}\text{Tc}$) injection (fission or 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 ($^{99m}\text{Tc}$) exametazime injection is a racemic mixture of (3RS, 9RS)-4, 8-diaza-3,6,6,9-tetramethylundecane-2,10-dione bisoxime (exametazime) complexes with sodium pertechnetate ($^{99m}\text{Tc}$) 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 ($^{99m}\text{Tc}$) exametazime complex.
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 140 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 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”. pH of the injection, between 5.0 to 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/V I.U of endotoxins per millilitre. The injection may be released for use before completion of the test.

Radionuclidic purity. Record the gamma-ray spectrum using a suitable instrument and measure the half-life using a suitable method. Determine the relative amounts of technetium-99m and radionuclidic impurities that may be present.

Radiochemical purity

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

A. Carry out three separate tests as described under 1.14.2 Paper chromatography and ascending conditions. Use suitable cellulose paper strips and methyl ethyl ketone R (system A) or sodium chloride (9 g/l) TS (system B) as the mobile phases. Use suitable silica gel impregnated glass fiber paper strips and a mixture of equal volumes of acetonitrile R and water R as the mobile phase (system C). Apply to the
paper about 5 μl of the injection to be examined, suitably diluted to give an optimum
count rate and develop for a distance of about 15 cm. Allow the paper to dry in air
and determine the radioactivity distribution by a suitable method. In system (A), the
secondary exametazime complex and reduced hydrolysed technetium-99m have Rf
value of 0, and the lipophilic exametazime complex and the pertechnetate ion have Rf
value of 0.8 to 1.0. In system (B), reduced hydrolysed technetium-99m has Rf value
of 0, and the lipophilic exametazime complex, the secondary exametazime complex
and the pertechnetate ion have an Rf value of 0.8 to 1.0. In system (C), the
pertechnetate ion has an Rf value of 0, and the lipophilic exametazime
complex, the secondary exametazime complex and reduced hydrolysed technetium-
99m have Rf value of 0. The sum of the percentages of radioactivity corresponding to
the pertechnetate ion in system (C) and reduced hydrolysed technetium-99m in
system (B) is less than 10%. Not less than 80% of the total technetium-99m
radioactivity is present as lipophilic exametazime complex.

B. 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 per cent of the total radioactivity.

C. 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
fiber 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. 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 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 size of the column used is (l =
0.25 m, Ø = 4.6 mm). The stationary phase is spherical base-deactivated end-capped
octadecylsilyl silica gel for chromatography R (5 µm) with a pore size of 13 nm and a carbon loading of 11 per cent. Mix 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 the run time is 20 min. The relative retention with reference to lipophilic technetium-99m exametazime to impurity A is about 1.2.

**System suitability: reference solution:**

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 per cent of the radioactivity due to lipophilic technetium-99m exametazime and impurity A.

**Chemical purity**

**Tin.** 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 (1 mol/l) VS and mixing thoroughly. Prepare the reference solution by dissolving 0.115 g of stannous chloride R in hydrochloric acid (1 mol/l) VS, diluting to 1000 ml with the same solvent and mixing thoroughly. 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 as described under R.1.1 Detection and measurement of radioactivity in a suitable calibrated counting equipment by comparison with a standardized technetium-99m solution or by measurement in an instrument calibrated with the aid of such a solution (a good approximation may be obtained using an ionization chamber and employing a standardized solution of cobalt-57 provided that correction for the differences in the radiations emitted are made). Standardized technetium-99m and cobalt-57 solutions are available from laboratories recognized by the relevant national or regional authority.
**Impurities**

![Chemical Structure](image)

**A.** Meso isomer of lipophilic technetium-99m exametazime,

**B.** Technetium-99m in colloidal form,

**C.** $[^{99m}Tc]$Pertechnetate ion,

**D.** Non lipophilic technetium-99m exametazime complex,

**E.** Meso isomer of non-lipophilic technetium-99m exametazime complex.

**Biodistribution.** Carry out the test as described under **R3.1 Biological distribution** using a set of three mice. At 5 to 10 minutes post injection not less than 1.5% of the injected radioactivity should be found in the brain and not more than 20% of the injected radioactivity should be found in the intestine. Not more than 15% of the injected radioactivity should be found in the liver.

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