**L-Methionine ([11C]methyl) injection**

**DEFINITION**
Sterile solution of (2S)-2-amino-4-([11C]methylsulphonyl)butanoic acid for diagnostic use.  

**Content:** 90 per cent to 110 per cent of the declared carbon-11 radioactivity at the date and time stated on the label.  

**Purity:**  
- minimum of 99 per cent of the total radioactivity corresponds to carbon-11,  
- minimum of 95 per cent of the total radioactivity corresponds to carbon-11 in the form of \( \Delta[11C] \)-methionine and \( \Delta[11C] \)-methionine,  
- maximum of 10 per cent of the total radioactivity corresponds to carbon-11 in the form of \( \Delta[11C] \)-methionine.  

**Content of methionine:** maximum of 2 mg per maximum recommended dose in millilitres.

**PRODUCTION**

**RADIONUCLIDE PRODUCTION**
Carbon-11 is a radioactive isotope of carbon which is most commonly produced by proton irradiation of nitrogen. Depending on the addition of either trace amounts of oxygen or small amounts of hydrogen, the radioactivity is obtained as \([\text{11C}] \)carbon dioxide or \([\text{11C}] \)methane.

**RADIOCHEMICAL SYNTHESIS**
L-[Methyl-\( ^{11} \)C]methionine can be prepared by various chemical synthetic pathways. All methods rely on the alkylation of the sulphide anion of L-homocysteine with \([\text{11C}] \)methyl iodide or \([\text{11C}] \)methyl triflate. Variations in the procedures used to generate the sulphide anion of L-homocysteine and methods to obtain \([\text{11C}] \)methyl iodide lead to negligible differences with respect to quality in terms of specific radioactivity, enantiomeric purity and possible chemical and radiochemical impurities.

**Synthesis of \([\text{11C}] \)methyl iodide**
\([\text{11C}] \)Methyl iodide can be obtained either starting from \([\text{11C}] \)carbon dioxide or from \([\text{11C}] \)methane. The most frequently used method is the reduction of \([\text{11C}] \)carbon dioxide with lithium aluminium hydride. The formed \([\text{11C}] \)methanol is reacted with hydroiodic acid. Alternatively \([\text{11C}] \)methane, either obtained directly in the target or by on-line processes from \([\text{11C}] \)carbon dioxide, is reacted with iodine.

**Synthesis of \([\text{11C}] \)methyl triflate**
\([\text{11C}] \)methyl triflate can be prepared from \([\text{11C}] \)methyl iodide using a silver triflate-impregnated solid support such as graphitised carbon.

**Synthesis of L-[methyl-\( ^{11} \)C]methionine**
The most widely used method to obtain L-[methyl-\( ^{11} \)C]methionine is the alkylation of the sulphide anion, generated from L-homocysteine thiolactone, with...
L-[Methyl-\( ^{11}\text{C} \)]methionine injection

[\text{\[^{11}\text{C} \text{methyl iodide or \[^{11}\text{C} \text{methyl triflate in alkaline conditions in a solvent such as acetone. The L-Methyl-\[^{11}\text{C} \text{methionine can be purified by semi-preparative liquid chromatography. For example, a column with octadecylsilyl silica gel for chromatography eluted with a 9 g/l solution of sodium chloride is suitable.} \]}

\text{1-Homocysteine thiolactone hydrochloride}

Specific optical rotation (2.2.7): +20.5 to +21.5, determined on a 10 g/l solution at 25 °C.

Infrared absorption spectrophotometry (2.2.24).

Comparison: Ph. Eur. reference spectrum of L-homocysteine thiolactone hydrochloride.

CHARACTERS

\text{Appearance:} clear, colourless solution.

\text{Half-life and nature of radiation of carbon-11:} see Table of physical characteristics of radionuclides (5.7).

IDENTIFICATION

A. Gamma-ray spectrometry. Results: the only gamma photons have an energy of 0.511 MeV and, depending on the measurement geometry, a sum peak of 1.022 MeV may be observed.

B. It complies with the test for radionuclidic purity (see Tests).

C. Examine the chromatograms obtained in the test for radiochemical purity. Results: the principal peak in the radiochromatogram obtained with the test solution is similar in retention time to the principal peak in the chromatogram obtained with reference solution (b).

TESTS

\text{pH (2.2.3):} 4.5 to 8.5.

\text{Sterility.} It complies with the test for sterility prescribed in the monograph on Radiopharmaceutical preparations (0125). The injection may be released for use before completion of the test.

\text{Bacterial endotoxins (2.6.14):} less than 175/V IU/ml, \( V \) being the maximum recommended dose in millilitres. The injection may be released for use before completion of the test.

\text{CHEMICAL PURITY}

\text{Impurity A, impurity B and methionine.} Liquid chromatography (2.2.29).

\text{Test solution.} The preparation to be examined.

\text{Reference solution (a).} Dissolve 0.6 mg of L-homocysteine thiolactone hydrochloride R, 2 mg of DL-homocysteine R and 2 mg of DL-methionine R in water R and dilute to 10 ml with the same solvent.

\text{Reference solution (b).} Dissolve 2 mg of L-methionine R in the same solvent as used in the test solution and dilute to 10 ml with the same solvent.

\text{Column:}

- \text{size:} 1 = 0.25 m, \( \phi = 4.6 \, \text{mm} \),
- \text{stationary phase:} spherical octadecylsilyl silica gel for chromatography R (5 μm) with a specific surface of 220 m\(^2\)/g, a pore size of 8 nm and a carbon loading of 6.2 per cent,
- \text{temperature:} 25 °C.

\text{Mobile phase:} 1.4 g/l solution of potassium dihydrogen phosphate R.

\text{Flow rate:} 1 ml/min.

\text{Detection:} spectrophotometer at 225 nm and radioactivity detector connected in series.

\text{Injection:} loop injector.

\text{Run time:} 10 min.

\text{Relative retention with reference to methionine (retention time = about 2.6 min):} impurity B = about 0.8, impurity A = about 2.7.

\text{System suitability:} reference solution (a):

- \text{resolution:} minimum of 2.5 between the peaks due to methionine and impurity B.

\text{Limits:} examine the chromatogram obtained with the spectrophotometer:

- \text{impurity A:} not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.6 mg/V),
- \text{impurity B:} not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (2 mg/V),
- \text{methionine:} not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (2 mg/V).

\text{Residual solvents (2.4.24):} maximum 50 mg/V for the concentration of acetone, \( V \) being the maximum recommended dose in millilitres. The preparation may be released for use before completion of the test.

\text{RADIONUCLIDIC PURITY}

\text{Carbon-11:} minimum 99 per cent of the total radioactivity.

A. Gamma-ray spectrometry.

\text{Comparison:} standardised fluorine-18 solution, or by using an instrument calibrated with the aid of such a solution. Standardised fluorine-18 solutions and/or standardisation services are available from the competent authority.

\text{Results:} the spectrum obtained with the solution to be examined does not differ significantly from that obtained with a standardised fluorine-18 solution.

B. Half-life: 19.9 min to 20.9 min.

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

\text{RADIOCHEMICAL PURITY}

\text{L-Methyl-\[^{11}\text{C} \text{methionine and impurity E.} Liquid chromatography (2.2.29) as described in the test for impurity A, impurity B and methionine.}

\text{Injection:} test solution and reference solution (b).

\text{Limits:} examine the chromatogram obtained with the radioactivity detector:

- \text{total of L-[methyl-\[^{11}\text{C} \text{methionine and impurity E:} minimum of 95 per cent of the total radioactivity,
- \text{other peaks in the chromatogram may be due to impurity C, impurity D and impurity F.}

\text{ENANTIOMERIC PURITY}

\text{Impurity E.} Thin-layer chromatography (2.2.27).

\text{Test solution.} The preparation to be examined.

\text{Reference solution (a).} Dissolve 2 mg of L-methionine R in water R and dilute to 10 ml with the same solvent.

\text{Reference solution (b).} Dissolve 4 mg of DL-methionine R in water R and dilute to 10 ml with the same solvent.

\text{Plate:} TLC octadecylsilyl silica gel plate for chiral separations R.

\text{Mobile phase:} methanol R, water R (50:50 V/V).

\text{Application:} 2-10 μl.

\text{Development:} over a path of 8 cm.
Norcholesterol injection, iodinated (131I)

DEFINITION
Iodinated (131I) norcholesterol injection is a sterile, bacterial endotoxin-free solution of 6β-[131I]iodomethyl-19-norcholest-5(10)-en-3β-ol. It may contain a suitable emulsifier such as polysorbate 80 and a suitable antimicrobial preservative such as benzyl alcohol. Iodine-131 is a radioactive isotope of iodine and may be obtained by neutron irradiation of tellurium or by extraction from uranium fission products. The injection contains not less than 90.0 per cent and not more than 110.0 per cent of the declared iodine-131 radioactivity at the date and hour stated on the label. Not less than 85 per cent of the radioactivity corresponds to iodine-131 in the form of 6β-[131I]iodomethyl-19-norcholest-5(10)-en-3β-ol. Not more than 5 per cent of the radioactivity corresponds to iodine-131 in the form of iodide. The specific radioactivity is 3.7 GBq to 37 GBq per gram of 6β-iodomethylnorcholesterol.

CHARACTERS
A clear or slightly turbid, colourless or pale yellow solution. Iodine-131 has a half-life of 8.04 days and emits beta and gamma radiation.

IDENTIFICATION
A. Record the gamma-ray spectrum using a suitable instrument. The spectrum does not differ significantly from that of a standardised iodine-131 solution by direct comparison with such a solution. The most prominent photon of iodine-131 has an energy of 0.365 MeV. Standardised iodine-131 solutions are available from laboratories recognised by the competent authority.

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

TESTS
pH (2.2.3). The pH of the solution is between 3.5 and 8.5.

Sterility. It complies with the test for sterility prescribed in the monograph on Radiopharmaceutical preparations (0125). The injection may be released for use before completion of the test.

Bacterial endotoxins (2.6.14): less than 175 VIU/ml, V being the maximum recommended dose in millilitres.

RADIONUCLIDIC PURITY
Record the gamma-ray spectrum using a suitable instrument. The spectrum does not differ significantly from that of a standardised iodine-131 solution. Determine the relative amounts of iodine-131, iodine-133, iodine-135 and other