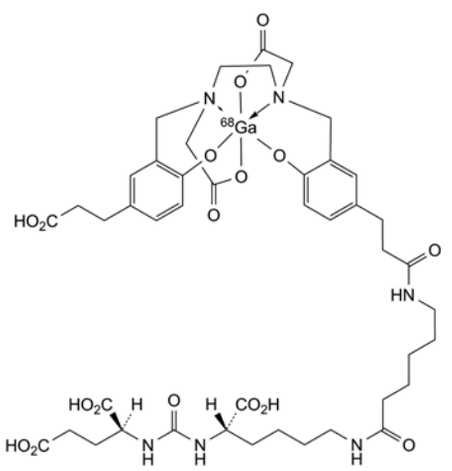
Reference: PA/PH/Exp. 14/T (16) 45 ANP

XXXX:3044

GALLIUM (^{68}Ga) PSMA-11 INJECTION

Gallii (^{68}Ga) PSMA-11 solutio iniectabilis



$C_{44}H_{58}{}^{68}GaN_6O_{17}$ M_r 1011

DEFINITION

Sterile solution of a complex of gallium-68 with the human prostate-specific membrane antigen (PSMA)-targeting ligand (3*S*,7*S*)-22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]-methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxyphenyl]-5,13,20-trioxo-4,6,12,19-tetraazodocosane-1,3,7-tricarboxylic acid (PSMA-11). It is prepared using *Gallium (^{68}Ga) chloride solution for radiolabelling (2464)* and PSMA-11. It may contain a suitable buffer.

Content:

– *gallium-68*: 90 per cent to 110 per cent of the declared gallium-68 radioactivity at the date and time stated on the label;

– *PSMA-11*: maximum 30 µg per maximum recommended dose in millilitres.

A reversible stereoisomerisation of [^{68}Ga]gallium PSMA-11 takes place in solution depending on temperature, pH and time.

CHARACTERS

Appearance: clear, colourless solution.

Half-life and nature of radiation of gallium-68: see general chapter *5.7. Table of physical characteristics of radionuclides*.

IDENTIFICATION

A. Gamma-ray spectrometry.

Result: the principal gamma photons have energies of 0.511 MeV and 1.077 MeV and, depending on the measurement geometry, a sum peak of 1.022 MeV may be observed; a peak corresponding to gamma photons with an energy of 1.883 MeV may be observed.

B. Approximate half-life: 62 min to 74 min.

C. Examine the chromatograms obtained in the test for impurities A and B and other radiochemical impurities (see Tests).

Result: the 2 principal peaks in the radiochromatogram obtained with the test solution are similar in retention time to the 2 principal peaks in the chromatogram obtained with reference solution (a) using the spectrophotometer.

TESTS

pH (*2.2.4*): 4 to 8.

PSMA-11, gallium PSMA-11 and other related substances. Liquid chromatography (*2.2.29*).

Solvent mixture: *trifluoroacetic acid R*, *water R* (1:999 *V/V*).

Test solution. The preparation to be examined.

Reference solution (a). Dissolve a quantity of *gallium PSMA-11 R* corresponding to 50 µg of anhydrous and trifluoroacetic acid-free gallium PSMA-11 in 1.0 mL of *water R*.

Reference solution (b). Dissolve a quantity of *PSMA-11 R* corresponding to 30 µg of anhydrous and trifluoroacetic acid-free PSMA-11 in the solvent mixture and dilute to *V* with the solvent mixture, *V* being the maximum recommended dose in millilitres.

Reference solution (c). Dilute 1.0 mL of reference solution (b) to 10.0 mL with the solvent mixture.

Column:

– *size*: *l* = 0.15 m, Ø = 3.0 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (3 µm)[(1)].

Mobile phase:

– *mobile phase A*: *trifluoroacetic acid R*,~~*water R*~~ *water for chromatography R* (1:999 *V/V*);

– *mobile phase B*: *trifluoroacetic acid R*, *acetonitrile R* (1:999 *V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 0.5	95	5
0.5 - 10	95 → 60	5 → 40
10 - 11	60 → 95	40 → 5
11 - 16	95	5

Flow rate: 0.6 mL/min.

Detection: spectrophotometer at 280 nm and radioactivity detector connected in series.

Injection: 20 µL.

Relative retention with reference to PSMA-11 (retention time = about 8 min): gallium PSMA-11 stereoisomer 1 = about 0.9; gallium PSMA-11 stereoisomer 2 = about 0.97.

System suitability: reference solution (a):

– *resolution*: minimum 1.5 between the peaks due to gallium PSMA-11 stereoisomers 1 and 2.

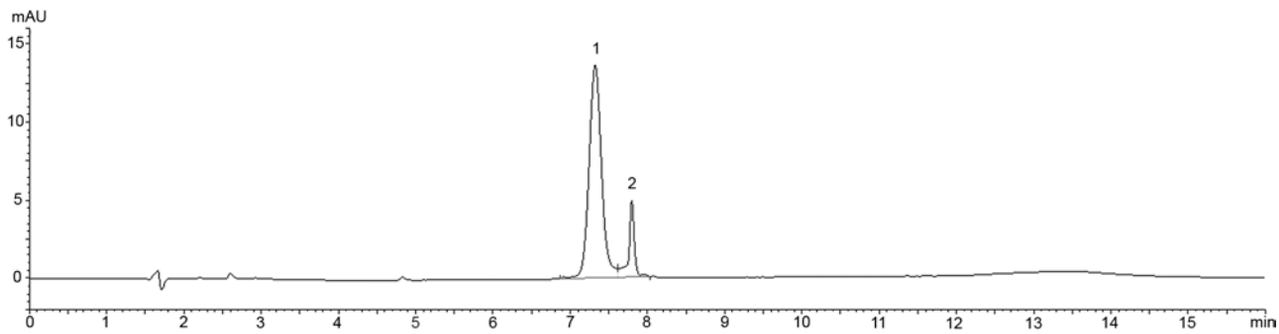
Limits: in the chromatogram obtained using the spectrophotometer:

– *PSMA-11, gallium PSMA-11 and other related substances* (the sum of the areas of the peaks due to compounds with a relative retention of not less than 0.8 and not more than 1.3 with reference to PSMA-11): not more than the area of the principal peak in the chromatogram obtained with reference solution (b) (30 µg/*V*);

– *disregard limit*: the area of the principal peak in the chromatogram obtained with reference solution (c) (3 µg/*V*).

(1) ACE 3 C18 base deactivated is suitable.

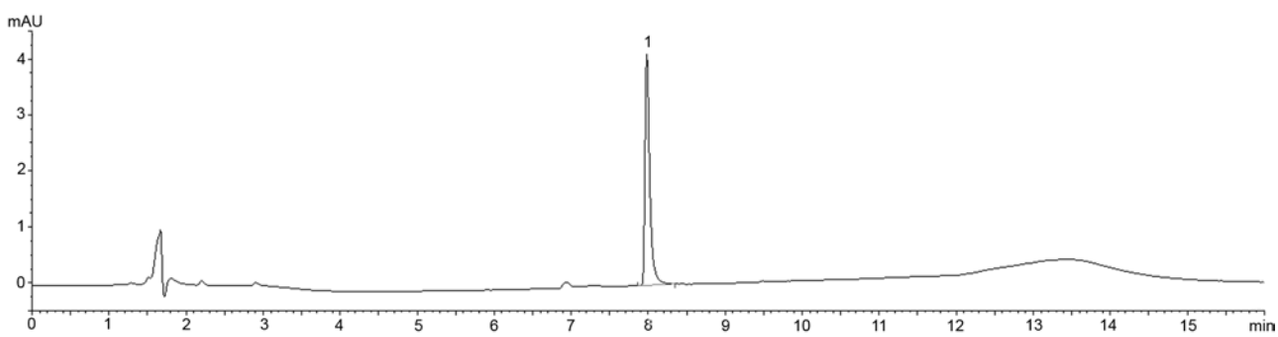
The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.



1. Gallium PSMA-11 stereoisomer 1
2. Gallium PSMA-11 stereoisomer 2

Figure 3044.-1. – *Chromatogram for the test for PSMA-11, gallium PSMA-11 and other related substances: reference solution (a).*

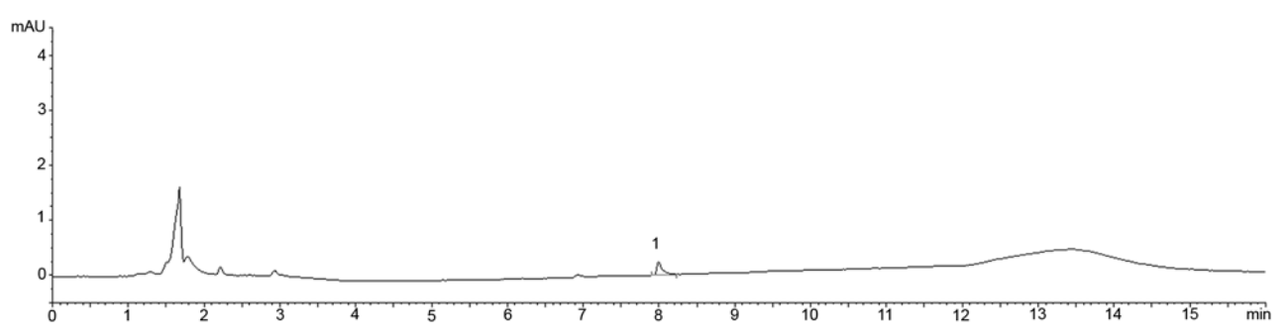
The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.



1. PSMA-11

Figure 3044.-2. – *Chromatogram for the test for PSMA-11, gallium PSMA-11 and other related substances: reference solution (b).*

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.



1. PSMA-11

Figure 3044.-3. – *Chromatogram for the test for PSMA-11, gallium PSMA-11 and other related substances: 10-fold dilution of reference solution (b).*

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

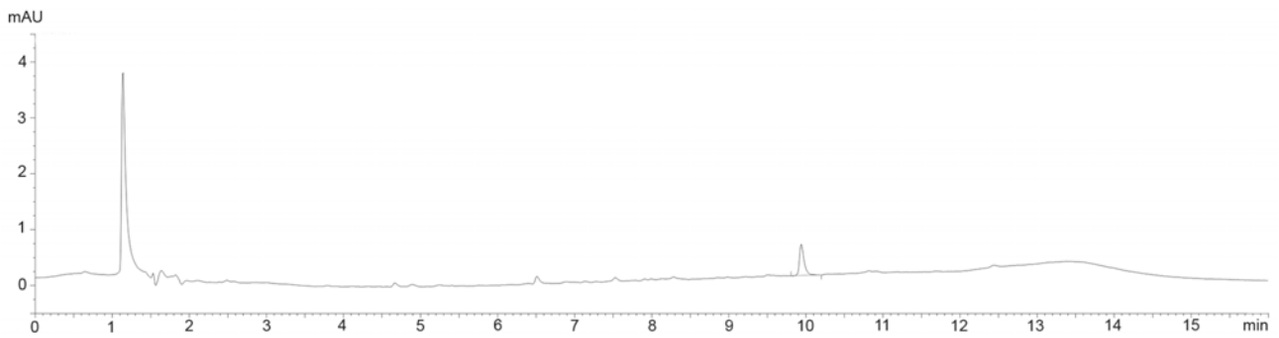


Figure 3044.-4. – *Chromatogram for the test for PSMA-11 gallium PSMA-11 and other related substances: typical chromatogram of a test solution (10 µg PSMA-11/V, V = 10 mL).*

Impurity C. Thin-layer chromatography (*2.2.27*).

Test solution. The preparation to be examined.

Reference solution. Dissolve 10 mg of *HEPES R* (impurity C) in *water R* and dilute to *V* with the same solvent, *V* being the maximum recommended dose in millilitres. Dilute 1.0 mL of the solution to 50.0 mL with *water R*.

Plate: *TLC silica gel F_{254} plate R*(2).

Mobile phase: *water R*, *acetonitrile R* (25:75 *V/V*).

Application: (*V*/1000 mL), *V* being the maximum recommended dose in millilitres; apply portions of 1 µL and dry with a current of warm air after each application.

Development: over 2/3 of the plate.

Detection: expose to iodine vapour for 4 min.

Retardation factor: impurity C = about 0.5.

System suitability: reference solution:

– the chromatogram shows a clearly visible spot.

Limit:

– *impurity C*: any spot due to impurity C is not more intense than the corresponding spot in the chromatogram obtained with the reference solution (200 µg/*V*).

Ethanol (*2.4.24* or another suitable, validated method): maximum 10 per cent *V/V* and maximum 2.5 g per administration, taking the density (*2.2.5*) to be 0.790 g/mL.

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

Bacterial endotoxins (*2.6.14*): less than 175/*V* IU/mL, *V* being the maximum recommended dose in millilitres. The preparation may be released for use before completion of the test.

RADIOCHEMICAL PURITY

[^{68}Ga]Gallium PSMA-11, impurities A and B and other radiochemical impurities. Liquid chromatography (*2.2.29*) as described in the test for PSMA-11, gallium PSMA-11 and other related substances. If necessary, dilute the test solution with *water R* to a radioactivity concentration suitable for the radioactivity detector.

Examine the chromatogram obtained using the radioactivity detector and locate the peaks due to [^{68}Ga]gallium PSMA-11 by comparison with the chromatogram obtained with reference solution (a) using the spectrophotometer.

Relative retention with reference to [^{68}Ga]gallium PSMA-11 stereoisomer 1 (retention time = about 7.5 min): impurities A and B = about 0.2.

(2) Merck ALUGRAM Xtra Nano SILGUR UV254 is suitable.

The following chromatogram is shown for information but will not be published in the European Pharmacopoeia.

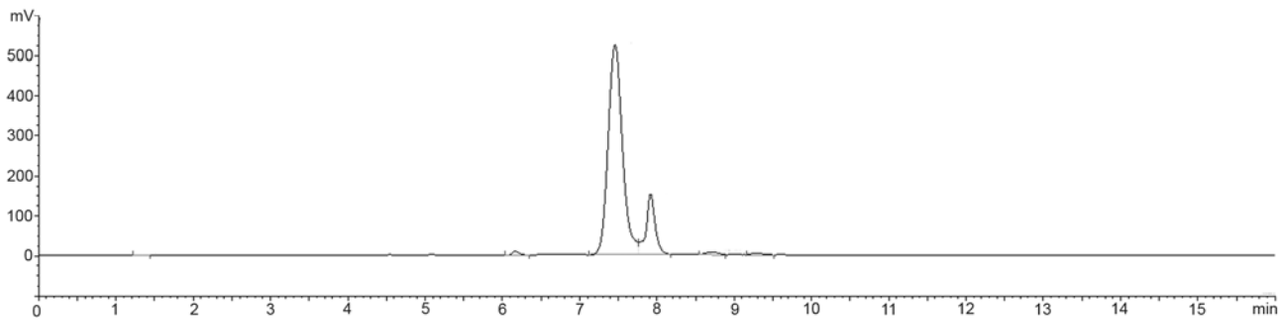


Figure 3044.-5. – *Chromatogram for the test for impurities A and B and other radiochemical impurities: typical radiochromatogram of a test solution.*

Limits:

– *sum of impurities A and B*: not more than 3 per cent of the total radioactivity due to gallium-68;

– *[^{68}Ga]gallium PSMA-11*: minimum 91 per cent of the total radioactivity due to gallium-68.

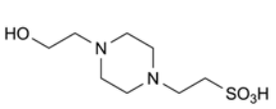
RADIOACTIVITY

Determine the radioactivity using a calibrated instrument.

IMPURITIES

A. [^{68}Ga]gallium in colloidal form,

B. [^{68}Ga]gallium(III) ion,



C. 2-[4-(2-hydroxyethyl)piperazin-1-yl]ethanesulfonic acid (HEPES).

Reagents

PSMA-11. $C_{44}H_{62}N_6O_{17}$. (M_r 947). *XXXXXXX.* [1366302-52-4]. (3*S*,7*S*)-22-[3-[[[2-[[[5-(2-Carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]-methyl]-4-hydroxyphenyl]-5,13,20-trioxo-4,6,12,19-tetraazodocosane-1,3,7-tricarboxylic acid supplied as trifluoroacetate salt.

White or almost white powder, freely soluble in water.

Content: minimum 96.0 per cent (anhydrous and trifluoroacetic acid-free substance).

Gallium PSMA-11. $C_{44}H_{58}GaN_6O_{17}$. (M_r 1013). *XXXXXXX.*
Complex of gallium with (3*S*,7*S*)-22-[3-[[[2-[[[5-(2-carboxyethyl)-2-hydroxyphenyl]methyl](carboxymethyl)amino]ethyl](carboxymethyl)amino]methyl]-4-hydroxy-phenyl]-5,13,20-trioxo-4,6,12,19-tetraazodocosane-1,3,7-tricarboxylic acid (PSMA-11).

Colourless or almost white powder.

Content: minimum 95.0 per cent (anhydrous and trifluoroacetic acid-free substance).