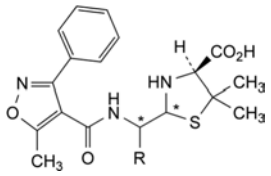
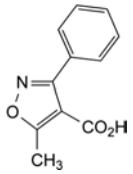
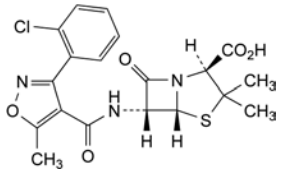


B. R = CO_2H: (4*S*)-2-[carboxy[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of oxacillin),

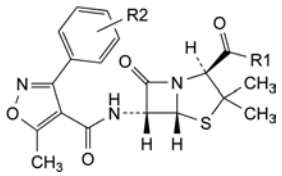
D. R = H: (2*RS*,4*S*)-5,5-dimethyl-2-[[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]methyl]thiazolidine-4-carboxylic acid (penilloic acids of oxacillin),



C. 5-methyl-3-phenylisoxazole-4-carboxylic acid,

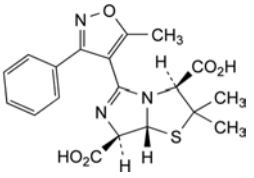


E. (2*S*,5*R*,6*R*)-6-[[[3-(2-chlorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (cloxacillin),

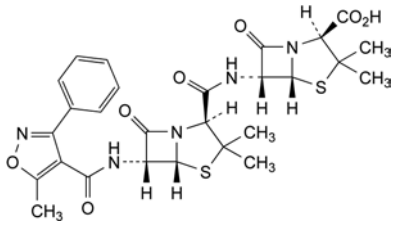


F. R1 = SH, R2 = H: (2*R*,5*R*,6*R*)-3,3-dimethyl-6-[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbothioic acid (thiooxacillin),

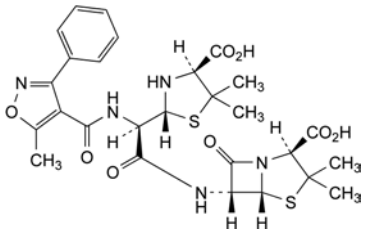
G. R1 = OH, R2 = Cl: (2*S*,5*R*,6*R*)-6-[[[3-(chlorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (cloxacillin isomer),



H. (3*S*,7*R*,7a*R*)-2,2-dimethyl-5-(5-methyl-3-phenylisoxazol-4-yl)-2,3,7,7a-tetrahydroimidazo[5,1-*b*]thiazole-3,7-dicarboxylic acid (penillic acid of oxacillin),



I. (2*S*,5*R*,6*R*)-6-[[(2*S*,5*R*,6*R*)-3,3-dimethyl-6-[[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-APA oxacillin amide),

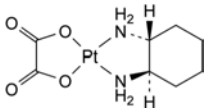


J. (2*S*,5*R*,6*R*)-6-[[(2*R*)-[(2*R*,4*S*)-4-carboxy-5,5-dimethylthiazolidin-2-yl][[(5-methyl-3-phenylisoxazol-4-yl)carbonyl]amino]acetyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (ozolamide of 6-APA dimer).

01/2009:2017
corrected 7.0

OXALIPLATIN

Oxaliplatinum



$C_8H_{14}N_2O_4Pt$ M_r 397.3
[61825-94-3]

DEFINITION

(*SP*-4-2)-[(1*R*,2*R*)-Cyclohexane-1,2-diamine-κ*N*,κ*N*′][ethanedioato(2-)-κO^1,κO^2]platinum.

Content: 98.0 per cent to 102.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: slightly soluble in water, very slightly soluble in methanol, practically insoluble in anhydrous ethanol.

IDENTIFICATION

A. Infrared absorption spectrophotometry (*2.2.24*).
Comparison: *oxaliplatin CRS*.

B. Specific optical rotation (see Tests).

TESTS

Appearance of solution. The solution is clear (*2.2.1*) and colourless (*2.2.2, Method II*).

Dissolve 0.10 g in *water R* and dilute to 50 mL with the same solvent.

Acidity. Dissolve 0.10 g in *carbon dioxide-free water R*, dilute to 50 mL with the same solvent and add 0.5 mL of *phenolphthalein solution R1*. The solution is colourless. Not more than 0.60 mL of *0.01 M sodium hydroxide* is required to change the colour of the indicator to pink.

Specific optical rotation (*2.2.7*): + 74.5 to + 78.0 (dried substance).

Dissolve 0.250 g in *water R* and dilute to 50.0 mL with the same solvent.

Related substances

A. Impurity A. Liquid chromatography (*2.2.29*). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.*

Test solution. Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 14.0 mg of *oxalic acid R* (impurity A) in *water R* and dilute to 250.0 mL with the same solvent.

Reference solution (b). Dilute 5.0 mL of reference solution (a) to 200.0 mL with *water R*.

Reference solution (c). Dissolve 12.5 mg of *sodium nitrate R* in *water R* and dilute to 250.0 mL with the same solvent. Dilute a mixture of 2.0 mL of this solution and 25.0 mL of reference solution (a) to 100.0 mL with *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase: mix 20 volumes of *acetonitrile R* with 80 volumes of a solution prepared as follows: to 10 mL of a 320 g/L solution of *tetrabutylammonium hydroxide R* add 1.36 g of *potassium dihydrogen phosphate R*, dilute to 1000 mL with *water R* and adjust to pH 6.0 with *phosphoric acid R*.

Flow rate: 2 mL/min.

Detection: spectrophotometer at 205 nm.

Injection: 20 µL of the test solution and reference solutions (b) and (c).

Run time: twice the retention time of impurity A.

Retention times: nitrate = about 2.7 min; impurity A = about 4.7 min.

System suitability:

– *resolution*: minimum 9 between the peaks due to nitrate and impurity A in the chromatogram obtained with reference solution (c);

– *signal-to-noise ratio*: minimum 10 for the peak due to impurity A in the chromatogram obtained with reference solution (b).

Limit:

– *impurity A*: not more than twice the area of the principal peak in the chromatogram obtained with reference solution (b) (0.1 per cent).

B. Impurity B. Liquid chromatography (*2.2.29*). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation. Use suitable polypropylene containers for the preparation and injection of all solutions. Glass pipettes may be used for diluting solutions.*

Test solution. Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Add 12.5 mg of *oxaliplatin impurity B CRS* to 63 mL of *methanol R* and dilute to 250.0 mL with *water R*. Sonicate for about 1.5 h until dissolved. Dilute 3.0 mL of this solution to 200.0 mL with *water R*.

Reference solution (b). In order to prepare impurity E *in situ*, add 12.5 mg of *oxaliplatin impurity B CRS* to 63 mL of *methanol R* and dilute to 250 mL with *water R*. Sonicate for about 1.5 h until dissolved. Adjust to pH 6.0 with a 0.2 g/L solution of *sodium hydroxide R*. Heat at 70 °C for 4 h and allow to cool.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *base-deactivated octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase: mix 20 volumes of *acetonitrile R* with 80 volumes of a solution prepared as follows: dissolve 1.36 g of *potassium dihydrogen phosphate R* and 1 g of *sodium heptanesulfonate R* in 1000 mL of *water R* and adjust to pH 3.0 ± 0.05 with *phosphoric acid R*.

Flow rate: 2.0 mL/min.

Detection: spectrophotometer at 215 nm.

Injection: 20 µL.

Run time: 2.5 times the retention time of impurity B.

Retention time: impurity B = about 4.3 min; impurity E = about 6.4 min.

System suitability:

– *resolution*: minimum 7 between the peaks due to impurities B and E in the chromatogram obtained with reference solution (b);

– *signal-to-noise ratio*: minimum 10 for the peak due to impurity B in the chromatogram obtained with reference solution (a).

Limit:

– *impurity B*: not more than 3.3 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.1 per cent).

C. Impurity C and other related substances. Liquid chromatography (*2.2.29*). *Use vigorous shaking and very brief sonication to dissolve the substance to be examined. Inject the test solution within 20 min of preparation.*

Test solution (a). Dissolve 0.100 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent.

Test solution (b). Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 500.0 mL with the same solvent.

Reference solution (a). Dissolve 10 mg of *oxaliplatin impurity C CRS* and 10 mg of *oxaliplatin CRS* in *water R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dilute 1.0 mL of reference solution (a) to 100.0 mL with *water R*.

Reference solution (c). Dissolve 5 mg of *dichlorodiamino-cyclohexaneplatinum CRS* in *methanol R* and dilute to 50.0 mL with the same solvent. To 10.0 mL of this solution add 10.0 mL of reference solution (a) and dilute to 100.0 mL with *water R*.

Reference solution (d). Dissolve 50.0 mg of *oxaliplatin CRS* in *water R* and dilute to 500.0 mL with the same solvent.

Reference solution (e). Dissolve 5.0 mg of *dichlorodiaminocyclohexaneplatinum CRS* in reference solution (d) and dilute to 50.0 mL with reference solution (d).

Reference solution (f). To 0.100 g of the substance to be examined add 1.0 mL of reference solution (a) and dilute to 50.0 mL with *water R*.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;

– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm);

– *temperature*: 40 °C.

Mobile phase: mix 1 volume of *acetonitrile R* with 99 volumes of a solution prepared as follows: dilute 0.6 mL of *dilute phosphoric acid R* in 1000 mL of *water R* and adjust to pH 3.0 with either *sodium hydroxide solution R* or *phosphoric acid R*.

Flow rate: 1.2 mL/min.

Detection: spectrophotometer at 210 nm.

Injection: 10 µL of test solution (a) and reference solutions (b), (c) and (f).

Run time: 3 times the retention time of oxaliplatin.

Retention time: impurity C = about 4.4 min; dichlorodiaminocyclohexaneplatinum = about 6.9 min; oxaliplatin = about 8.0 min.

System suitability:
- *resolution*: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (c);
- *signal-to-noise ratio*: minimum 50 for the peak due to impurity C and minimum 10 for the peak due to oxaliplatin in the chromatogram obtained with reference solution (b).

Limits:
- *impurity C*: not more than 0.5 times the area of the peak due to impurity C in the chromatogram obtained with reference solution (f) (0.1 per cent);
- *any other impurity*: not more than twice the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *total of other impurities*: not more than twice the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.1 per cent);
- *disregard limit*: the area of the peak due to oxaliplatin in the chromatogram obtained with reference solution (b) (0.05 per cent); disregard any peak with a retention time less than 2 min.

D. Total of impurities: the sum of impurities A, B, C and other related impurities is not greater than 0.30 per cent.

Impurity D. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 30 mg of the substance to be examined in *methanol R* and dilute to 50.0 mL with the same solvent.

Reference solution (a). Dissolve 5 mg of *oxaliplatin impurity D CRS* in *methanol R* and dilute to 100.0 mL with the same solvent.

Reference solution (b). Dilute 15.0 mL of reference solution (a) to 50.0 mL with *methanol R*.

Reference solution (c). Dissolve 150.0 mg of *oxaliplatin CRS* in *methanol R* and dilute to 200.0 mL with the same solvent.

Reference solution (d). Dilute 5.0 mL of reference solution (c) to 100.0 mL with *methanol R*.

Reference solution (e). To 40 mL of reference solution (c) add 1.0 mL of reference solution (b) and dilute to 50.0 mL with *methanol R*.

Reference solution (f). To 4.0 mL of reference solution (a) add 5.0 mL of reference solution (d) and dilute to 50.0 mL with *methanol R*.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *silica gel OC for chiral separations R*;
- *temperature*: 40 °C.

Mobile phase: *anhydrous ethanol R, methanol R* (30:70 *V/V*).

Flow rate: 0.3 mL/min.

Detection: spectrophotometer at 254 nm.

Injection: 20 µL of the test solution and reference solutions (e) and (f).

Run time: twice the retention time of oxaliplatin.

Retention time: oxaliplatin = about 14 min; impurity D = about 16 min.

System suitability:
- *resolution*: minimum 1.5 between the peaks due to oxaliplatin and impurity D in the chromatogram obtained with reference solution (f);
- *signal-to-noise ratio*: minimum 10 for the peak due to impurity D in the chromatogram obtained with reference solution (e).

Limit:
- *impurity D*: not more than twice the peak height of the corresponding peak in the chromatogram obtained with reference solution (e) (0.1 per cent).

Silver: maximum 5 ppm.

Atomic absorption spectrometry (*2.2.23, Method II*).

Test solution. Dissolve 0.1000 g of the substance to be examined in *water R* and dilute to 50.0 mL with the same solvent. Dilute 20 µL of this solution to 40 µL with *0.5 M nitric acid*.

Reference solution (a). Dilute a solution of *silver nitrate R* containing 1000 ppm of silver in *0.5 M nitric acid* with *0.5 M nitric acid* to obtain a solution which contains 10 ppb of silver.

Reference solution (b). Mix 20 µL of the test solution and 8 µL of reference solution (a) and dilute to 40 µL with *0.5 M nitric acid*.

Reference solution (c). Mix 20 µL of the test solution and 16 µL of reference solution (a) and dilute to 40 µL with *0.5 M nitric acid*.

Source: silver hollow-cathode lamp.

Wavelength: 328.1 nm.

Atomisation device: furnace.

Measure the absorbance of the test solution and reference solutions (b) and (c).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C for 2 h.

Bacterial endotoxins (*2.6.14*): less than 1.0 IU/mg, if intended for use in the manufacture of parenteral preparations without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

Liquid chromatography (*2.2.29*) as described in the test for impurity C and other related substances with the following modifications.

Injection: 20 µL of test solution (b) and reference solutions (d) and (e).

System suitability:
- *resolution*: minimum 2.0 between the peaks due to dichlorodiaminocyclohexaneplatinum and oxaliplatin in the chromatogram obtained with reference solution (e),
- *repeatability*: reference solution (d).

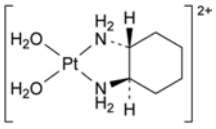
Calculate the percentage content of oxaliplatin using the chromatogram obtained with reference solution (d).

IMPURITIES

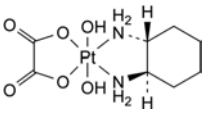
Specified impurities: A, B, C, D.

Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph *Substances for pharmaceutical use (2034)*. It is therefore not necessary to identify these impurities for demonstration of compliance. See also *5.10. Control of impurities in substances for pharmaceutical use*): *E.*

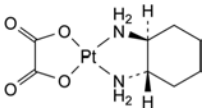
A. ethanedioic acid (oxalic acid),



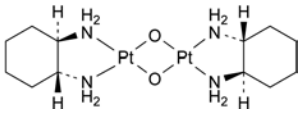
B. (*SP*-4-2)-diaqua[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*,κ*N*′]platinum (diaquodiaminocyclohexaneplatinum),



C. (*OC*-6-33)-[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*,κ*N*′][ethanedioato(2-)-κ*O*^{1},κ*O*^{2}]dihydroxyplatinum,



D. (*SP*-4-2)-[(1*S*,2*S*)-cyclohexane-1,2-diamine-κ*N*, κ*N*′][ethanedioato(2-)-κ*O*^{1},κ*O*^{2}]platinum (*S,S*-enantiomer of oxaliplatin),

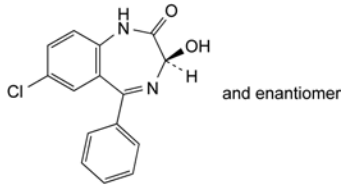


E. (*SP*-4-2)-di-μ-oxobis[(1*R*,2*R*)-cyclohexane-1,2-diamine-κ*N*,κ*N*′]diplatinum (diaquodiaminocyclohexaneplatinum dimer).

01/2008:0778
corrected 6.0

OXAZEPAM

Oxazepamum



$C_{15}H_{11}ClN_2O_2$ M_r 286.7
[604-75-1]

DEFINITION

(3*RS*)-7-Chloro-3-hydroxy-5-phenyl-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one.

Content: 99.0 per cent to 101.0 per cent (dried substance).

CHARACTERS

Appearance: white or almost white, crystalline powder.

Solubility: practically insoluble in water, slightly soluble in ethanol (96 per cent).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *oxazepam CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*). *Prepare the solutions immediately before use.*

Test solution. Dissolve 40.0 mg of the substance to be examined in 25 mL of a mixture of equal volumes of *acetonitrile R* and *water R* and dilute to 50.0 mL with the same mixture of solvents.

Reference solution (a). Dilute 1.0 mL of the test solution to 100.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*. Dilute 2.0 mL of this solution to 10.0 mL with a mixture of equal volumes of *acetonitrile R* and *water R*.

Reference solution (b). Dissolve the contents of a vial of *oxazepam for peak identification CRS* (containing impurities A, B, C, D and E) in 1.0 mL of the test solution.

Column:

– *size*: *l* = 0.25 m, Ø = 4.6 mm;
– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 μm) resistant to bases up to pH 11.

Mobile phase:

– *mobile phase A*: dissolve 3.48 g of *dipotassium hydrogen phosphate R* in 900 mL of *water R*, adjust to pH 10.5 with a 40 g/L solution of *sodium hydroxide R* and dilute to 1000 mL with *water R*;
– *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 4	75	25
4 - 34	75 → 25	25 → 75
34 - 45	25	75
45 - 50	25 → 75	75 → 25
50 - 60	75	25

Flow rate: 1.0 mL/min.

Detection: spectrophotometer at 235 nm.

Injection: 10 μL.

Identification of impurities: use the chromatogram obtained with reference solution (b) and the chromatogram supplied with *oxazepam for peak identification CRS* to identify the peaks due to impurities A, B, C, D and E.

Relative retention with reference to oxazepam (retention time = about 15 min): impurity E = about 0.7; impurity A = about 0.8; impurity B = about 1.2; impurity C = about 1.4; impurity D = about 2.0.

System suitability: reference solution (b):

– *resolution*: minimum 1.5 between the peaks due to impurities E and A.

Limits:

– *correction factors*: for the calculation of content, multiply the peak areas of the following impurities by the corresponding correction factor: impurity A = 4.0; impurity B = 1.1;
– *impurities A, B, C, D, E*: for each impurity, not more than the area of the principal peak in the chromatogram obtained with reference solution (a) (0.2 per cent);
– *unspecified impurities*: for each impurity, not more than 0.5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.10 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (a) (1.0 per cent);
– *disregard limit*: 0.25 times the area of the principal peak in the chromatogram obtained with reference solution (a) (0.05 per cent).

Loss on drying (*2.2.32*): maximum 0.5 per cent, determined on 1.000 g by drying in an oven at 105 °C at a pressure not exceeding 0.7 kPa.

Sulfated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g.

ASSAY

Dissolve 0.250 g in a mixture of 10 mL of *anhydrous acetic acid R* and 90 mL of *acetic anhydride R*. Titrate with *0.1 M perchloric acid*, determining the end-point potentiometrically (*2.2.20*).

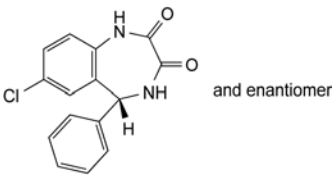
1 mL of *0.1 M perchloric acid* is equivalent to 28.67 mg of $C_{15}H_{11}ClN_2O_2$.

STORAGE

Protected from light.

IMPURITIES

Specified impurities: A, B, C, D, E.



A. (5*RS*)-7-chloro-5-phenyl-4,5-dihydro-1*H*-1,4-benzodiazepine-2,3-dione,