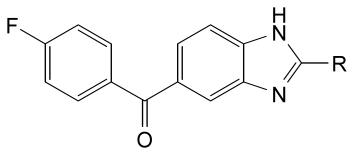


B. R = NH_2: (2-amino-1*H*-benzimidazol-5-yl)(4-fluorophenyl)methanone,

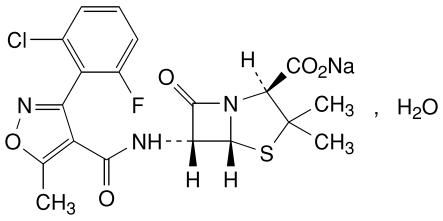
C. R = OH: (4-fluorophenyl)(2-hydroxy-1*H*-benzimidazol-5-yl)methanone,

D. R = H: (1*H*-benzimidazol-5-yl)(4-fluorophenyl)methanone.

01/2008:0668
corrected 6.0

FLUCLOXACILLIN SODIUM

Flucloxacillinum natricum



$C_{19}H_{16}ClFN_3NaO_5S,H_2O$ M_r 493.9

DEFINITION

Sodium (2*S*,5*R*,6*R*)-6-[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylate monohydrate.

Semi-synthetic product derived from a fermentation product.

Content: 95.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: freely soluble in water and in methanol, soluble in ethanol (96 per cent).

IDENTIFICATION

First identification: A, D.

Second identification: B, C, D.

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

B. Thin-layer chromatography (*2.2.27*).
Test solution. Dissolve 25 mg of the substance to be examined in 5 ml of *water R.*
Reference solution (a). Dissolve 25 mg of *flucloxacillin sodium CRS* in 5 ml of *water R.*
Reference solution (b). Dissolve 25 mg of *cloxacillin sodium CRS,* 25 mg of *dicloxacillin sodium CRS* and 25 mg of *flucloxacillin sodium CRS* in 5 ml of *water R.*
Plate: *TLC silanised silica gel plate R.*
Mobile phase: mix 30 volumes of *acetone R* and 70 volumes of a 154 g/l solution of *ammonium acetate R* adjusted to pH 5.0 with *glacial acetic acid R.*
Application: 1 µl.
Development: over a path of 15 cm.
Drying: in air.
Detection: expose to iodine vapour until the spots appear and examine in daylight.
System suitability: reference solution (b):
– the chromatogram shows 3 clearly separated spots.
Results: the principal spot in the chromatogram obtained with the test solution is similar in position, colour and size to the principal spot in the chromatogram obtained with reference solution (a).

C. Place about 2 mg in a test-tube about 150 mm long and 15 mm in diameter. Moisten with 0.05 ml of *water R* and add 2 ml of *sulphuric acid-formaldehyde reagent R.* Mix the contents of the tube by swirling; the colour of the solution is slightly greenish-yellow. Place the test-tube in a water-bath for 1 min; the solution becomes yellow.

D. It gives reaction (a) of sodium (*2.3.1*).

TESTS

Solution S. Dissolve 2.50 g in *carbon dioxide-free water R* and dilute to 25.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and its absorbance (*2.2.25*) at 430 nm is not greater than 0.04.

pH (*2.2.3*): 5.0 to 7.0 for solution S.

Specific optical rotation (*2.2.7*): + 158 to + 168 (anhydrous substance).

Dissolve 0.250 g in *water R* and dilute to 25.0 ml with the same solvent.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in the mobile phase and dilute to 50.0 ml with the mobile phase.

Test solution (b). Dilute 5.0 ml of test solution (a) to 50.0 ml with the mobile phase.

Reference solution (a). Dissolve 50.0 mg of *flucloxacillin sodium CRS* in the mobile phase and dilute to 50.0 ml with the mobile phase. Dilute 5.0 ml of this solution to 50.0 ml with the mobile phase.

Reference solution (b). Dilute 5.0 ml of reference solution (a) to 50.0 ml with the mobile phase.

Reference solution (c). Dissolve 5 mg of *flucloxacillin sodium CRS* and 5 mg of *cloxacillin sodium CRS* in the mobile phase, then dilute to 50.0 ml with the mobile phase.

Column:
– *size*: *l* = 0.25 m, Ø = 4 mm;
– *stationary phase*: *octadecylsilyl silica gel for chromatography R* (5 µm).

Mobile phase: mix 25 volumes of *acetonitrile R1* and 75 volumes of a 2.7 g/l solution of *potassium dihydrogen phosphate R* adjusted to pH 5.0 with *dilute sodium hydroxide solution R.*

Flow rate: 1 ml/min.

Detection: spectrophotometer at 225 nm.

Injection: 20 µl of test solution (a) and reference solutions (b) and (c).

Run time: 6 times the retention time of flucloxacillin.

System suitability: reference solution (c):
– *resolution*: minimum 2.5 between the peaks due to cloxacillin (1st peak) and flucloxacillin (2nd peak).

Limits:
– *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 (b) (1 per cent);
– *total*: not more than 5 times the area of the principal peak in the chromatogram obtained with reference solution (b) (5 per cent);

– *disregard limit*: 0.05 times the area of the principal peak in the chromatogram obtained with reference solution (b) (0.05 per cent).

***N,N*-Dimethylaniline** (*2.4.26, Method B*): maximum 20 ppm.

2-Ethylhexanoic acid (*2.4.28*): maximum 0.8 per cent *m/m*.

Water (*2.5.12*): 3.0 per cent to 4.5 per cent, determined on 0.300 g.

Pyrogens (*2.6.8*). If intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of pyrogens, it complies with the test. Inject per kilogram of the rabbit's mass 1 ml of a solution in *water for injections R* containing 20 mg of the substance to be examined per millilitre.

ASSAY

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

Injection: test solution (b) and reference solution (a).

System suitability: reference solution (a):

– *repeatability*: maximum relative standard deviation of 1.0 per cent after 6 injections.

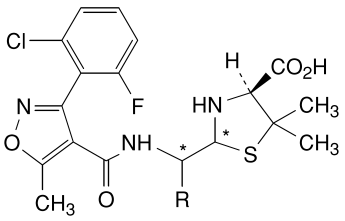
Calculate the percentage content of $C_{19}H_{16}ClFN_3NaO_5S$ from the declared content of *flucloxacillin sodium CRS*.

STORAGE

In an airtight container, at a temperature not exceeding 25 °C. If the substance is sterile, store in a sterile, airtight, tamper-proof container.

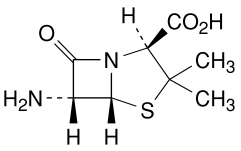
IMPURITIES

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

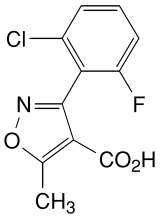


A. R = CO_2H: (4*S*)-2-[carboxy[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penicilloic acids of flucloxacillin),

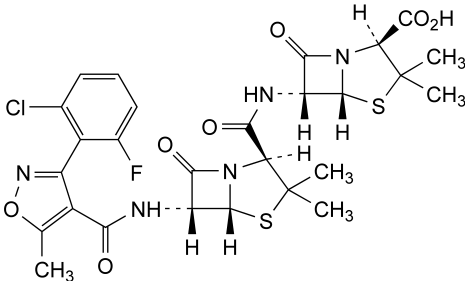
B. R = H: (2*RS*,4*S*)-2-[[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]methyl]-5,5-dimethylthiazolidine-4-carboxylic acid (penilloic acids of flucloxacillin),



C. (2*S*,5*R*,6*R*)-6-amino-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid (6-aminopenicillanic acid),



D. 3-(2-chloro-6-fluorophenyl)-5-methylisoxazole-4-carboxylic acid,

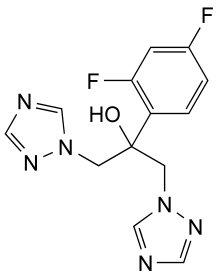


E. (2*S*,5*R*,6*R*)-6-[[[(2*S*,5*R*,6*R*)-6-[[[3-(2-chloro-6-fluorophenyl)-5-methylisoxazol-4-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]hept-2-yl]carbonyl]amino]-3,3-dimethyl-7-oxo-4-thia-1-azabicyclo[3.2.0]heptane-2-carboxylic acid.

01/2008:2287
corrected 6.0

FLUCONAZOLE

Fluconazolum



$C_{13}H_{12}F_2N_6O$ M_r 306.3
[86386-73-4]

DEFINITION

2-(2,4-Difluorophenyl)-1,3-bis(1*H*-1,2,4-triazol-1-yl)propan-2-ol.

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

CHARACTERS

Appearance: white or almost white, hygroscopic, crystalline powder.

Solubility: slightly soluble in water, freely soluble in methanol, soluble in acetone.

It shows polymorphism (*5.9*).

IDENTIFICATION

Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *fluconazole CRS*.