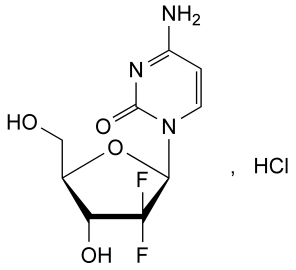
LABELLING

The label states the gel strength (Bloom value) or that it is a non-gelling grade.

01/2008:2306

GEMCITABINE HYDROCHLORIDE

Gemcitabini hydrochloridum



$C_9H_{12}ClF_2N_3O_4$ M_r 299.7

[122111-03-9]

DEFINITION

4-Amino-1-(2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl)pyrimidin-2(1*H*)-one hydrochloride.

Content: 98.0 per cent to 102.0 per cent.

CHARACTERS

Appearance: white or almost white powder.

Solubility: soluble in water, slightly soluble in methanol, practically insoluble in acetone.

IDENTIFICATION

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

B. It gives reaction (a) of chlorides (*2.3.1*).

TESTS

Solution S. Dissolve 1.00 g in *carbon dioxide-free water R* and dilute to 100.0 ml with the same solvent.

Appearance of solution. Solution S is clear (*2.2.1*) and not more intensely coloured than reference solution BY_7 (*2.2.2, Method II*).

pH (*2.2.3*): 2.0 to 3.0 for solution S.

Specific optical rotation (*2.2.7*): + 43.0 to + 50.0, determined on solution S.

Related substances. Liquid chromatography (*2.2.29*).

Test solution (a). Dissolve 50.0 mg of the substance to be examined in *water R* and dilute to 25.0 ml with the same solvent.

Test solution (b). Dissolve 20.0 mg of the substance to be examined in *water R* and dilute to 200.0 ml with the same solvent.

Reference solution (a). Dissolve 10.0 mg of the substance to be examined and 10.0 mg of *gemcitabine impurity A CRS* in *water R* and dilute to 50.0 ml with the same solvent. Dilute 2.0 ml of this solution to 200.0 ml with *water R*.

Reference solution (b). Dissolve 20.0 mg of *gemcitabine hydrochloride CRS* in *water R* and dilute to 200.0 ml with the same solvent.

Reference solution (c). Place 10 mg of the substance to be examined in a small vial. Add 4 ml of a 168 g/l solution of *potassium hydroxide R* in *methanol R*, sonicate for 5 min then seal with a cap. The mixture may be cloudy. Heat at 55 °C for a minimum of 6 h to produce impurity B. Allow to cool, then transfer the entire contents of the vial to a 100 ml volumetric flask by successively washing with a 1 per cent *V/V* solution of *phosphoric acid R*. Dilute to 100 ml with a 1 per cent *V/V* solution of *phosphoric acid R* and mix.

Column:
- *size*: *l* = 0.25 m, Ø = 4.6 mm;
- *stationary phase*: *octylsilyl silica gel for chromatography R* (5 µm).

Mobile phase:
- *mobile phase A*: 13.8 g/l solution of *sodium dihydrogen phosphate monohydrate R* adjusted to pH 2.5 ± 0.1 with *phosphoric acid R*;
- *mobile phase B*: *methanol R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 8	97	3
8 - 13	97 → 50	3 → 50
13 - 20	50	50

Flow rate: 1.2 ml/min.

Detection: spectrophotometer at 275 nm.

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

Relative retention with reference to gemcitabine (retention time = about 8 min): impurity A = about 0.4; impurity B = about 0.7.

System suitability: reference solution (c):
- *resolution*: minimum 8.0 between the peaks due to impurity B and gemcitabine.

Limits:
- *impurity A*: not more than the area of the corresponding peak in the chromatogram obtained with reference solution (a) (0.1 per cent);
- *unspecified impurities*: for each impurity, not more than the area of the peak due to gemcitabine in the chromatogram obtained with reference solution (a) (0.10 per cent);
- *total*: not more than twice the area of the peak due to gemcitabine in the chromatogram obtained with reference solution (a) (0.2 per cent);
- *disregard limit*: 0.5 times the area of the peak due to gemcitabine in the chromatogram obtained with reference solution (a) (0.05 per cent).

Heavy metals (*2.4.8*): maximum 10 ppm.

Dissolve 1.0 g in *water R* and dilute to 20 ml with the same solvent. 12 ml of the solution complies with test A. Prepare the reference solution using 5 ml of *lead standard solution (1 ppm Pb) R*, 5 ml of *water R* and 2 ml of the aqueous solution to be examined. If necessary, filter the solutions and compare the spots on the membrane filter.

Sulphated ash (*2.4.14*): maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

Bacterial endotoxins (*2.6.14*): less than 0.05 IU/mg, if intended for use in the manufacture of parenteral dosage forms without a further appropriate procedure for the removal of bacterial endotoxins.

ASSAY

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

Mobile phase: mobile phase A.

Injection: test solution (b) and reference solutions (b) and (c).

Relative retention with reference to gemcitabine (retention time = about 10 min): impurity B = about 0.5.

System suitability: reference solution (c):

– *resolution*: minimum 8.0 between the peaks due to impurity B and gemcitabine.

Calculate the percentage content of $C_9H_{12}ClF_2N_3O_4$ from the declared content of *gemcitabine hydrochloride CRS*.

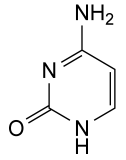
STORAGE

If the substance is sterile, store in a sterile, airtight, tamper-proof container.

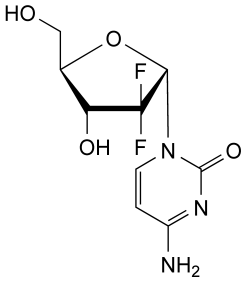
IMPURITIES

Specified impurities: A.

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*): *B.*



A. 4-aminopyrimidin-2(1*H*)-one (cytosine),

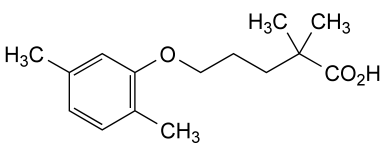


B. 4-amino-1-(2-deoxy-2,2-difluoro-α-D-*erythro*-pentofuranosyl)pyrimidin-2(1*H*)-one (gemcitabine α-anomer).

01/2008:1694

GEMFIBROZIL

Gemfibrozilum



$C_{15}H_{22}O_3$ M_r 250.3

[25812-30-0]

DEFINITION

5-(2,5-Dimethylphenoxy)-2,2-dimethylpentanoic acid.

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

CHARACTERS

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

Solubility: practically insoluble in water, very soluble in methylene chloride, freely soluble in anhydrous ethanol and in methanol.

IDENTIFICATION

A. Melting point (*2.2.14*): 58 °C to 61 °C.

B. Infrared absorption spectrophotometry (*2.2.24*).

Comparison: *gemfibrozil CRS*.

TESTS

Related substances. Liquid chromatography (*2.2.29*).

Test solution. Dissolve 40 mg of the substance to be examined in mobile phase A and dilute to 10.0 ml with mobile phase A.

Reference solution (a). Dissolve the contents of a vial of *gemfibrozil for system suitability CRS* (containing impurities C, D and E) in 2 ml of *acetonitrile R*.

Reference solution (b). Dilute 1.0 ml of test solution to 100.0 ml with mobile phase A. Dilute 1.0 ml of this solution to 10.0 ml with mobile phase A.

Reference solution (c). Dissolve 5 mg of *2,5-dimethylphenol R* (impurity A) in mobile phase A and dilute to 10 ml with mobile phase A.

Column:

– *size*: *l* = 0.250 m, Ø = 4.0 mm,

– *stationary phase*: *end-capped octadecylsilyl silica gel for chromatography R* (5 μm).

Mobile phase:

– *mobile phase A*: dissolve 0.27 g of *potassium dihydrogen phosphate R* in 400 ml of *water R*, adjust to pH 4.0 with *phosphoric acid R* and add 600 ml of *acetonitrile R*;

– *mobile phase B*: *acetonitrile R*;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 20	100 → 0	0 → 100
20 - 25	0	100
25 - 30	0 → 100	100 → 0
30 - 35	100	0

Flow rate: 1.5 ml/min.

Detection: spectrophotometer at 276 nm.

Injection: 20 μl.

Identification of impurities: use the chromatogram supplied with *gemfibrozil for system suitability CRS* and the chromatogram obtained with reference solution (a) to identify the peaks due to impurities C, D and E. Use the chromatogram obtained with reference solution (c) to identify the peak due to impurity A.

Relative retention with reference to gemfibrozil (retention time = about 7 min): impurity A = about 0.4; impurity C = about 1.3; impurity D = about 1.5; impurity E = about 1.7; impurity I = about 2.0; impurity H = about 2.9.

System suitability: reference solution (a):

– *resolution*: minimum 6.0 between the peaks due to gemfibrozil and impurity C, and minimum 2.0 between the peaks due to impurity D and impurity E.