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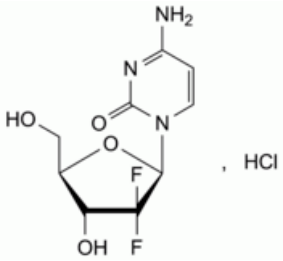
Edition: BP 2025 (Ph. Eur. 11.6 update)

Gemcitabine Hydrochloride

General Notices

(Ph. Eur. monograph 2306)



$C_9H_{12}ClF_2N_3O_4$ 299.7 *122111-03-9*

Action and use

Pyrimidine analogue; cytotoxic.

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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).

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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 1.0 mL of the solution to 100.0 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) In order to prepare impurity B *in situ*, 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. 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.

Reference solution (d) Dissolve 10.0 mg of gemcitabine impurity C CRS in water R and dilute to 25.0 mL with the same solvent. Dilute 1.0 mL of the solution to 100.0 mL with water R.

Column:

— *size*: *l* = 0.25 m, Ø = 4.6 mm;

— *stationary phase*: base-deactivated 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;

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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), (c) and (d).

Identification of impurities Use the chromatogram obtained with reference solution (a) to identify the peak due to impurity A; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity B; use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C.

Relative retention With reference to gemcitabine (retention time = about 7 min): impurity A = about 0.4; impurity B = about 0.7; impurity C = about 1.7.

System suitability Reference solution (c):

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

Calculation of percentage contents:

— for impurity C, use the concentration of impurity C in reference solution (d);

— for impurity A, use the concentration of impurity A in reference solution (a);

— for impurities other than A and C, use the concentration of gemcitabine hydrochloride in reference solution (a).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *impurity A*: maximum 0.15 per cent;

— *unspecified impurities*: for each impurity, maximum 0.10 per cent;

— *total*: maximum 0.4 per cent;

— *reporting threshold*: 0.05 per cent.

Sulfated ash (*2.4.14*)

Maximum 0.1 per cent, determined on 1.0 g in a platinum crucible.

ASSAY

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

Mobile phase *methanol R*, mobile phase A (3:97 *V/V*).

Injection Test solution (b) and reference solution (b).

Relative retention With reference to gemcitabine (retention time = about 8 min): impurity B = about 0.5.

Calculate the percentage content of $C_9H_{12}ClF_2N_3O_4$ taking into account the assigned content of *gemcitabine hydrochloride CRS*.

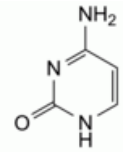
STORAGE

In an airtight container. If the substance is sterile, the container is also sterile and tamper-evident.

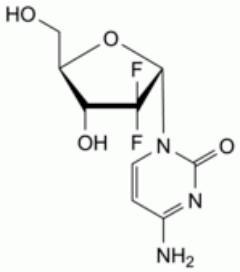
IMPURITIES

Specified impurities *A, C.*

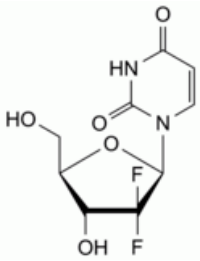
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical 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),



C. 1-(2-deoxy-2,2-difluoro-β-D-*erythro*-pentofuranosyl)pyrimidin-2,4(1*H*,3*H*)-dione (2′-deoxy-2′,2′-difluorouridine).

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