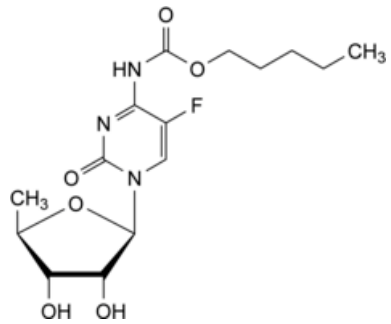
Edition: BP 2025 (Ph. Eur. 11.6 update)

Capecitabine

General Notices

(Ph. Eur. monograph 2762)



$C_{15}H_{22}FN_3O_6$ 359.3 *154361-50-9*

Action and use

Pyrimidine analogue; cytotoxic; treatment of colorectal cancer.

Preparation

Capecitabine Tablets

Ph Eur

DEFINITION

Pentyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate.

Content

98.0 per cent to 102.0 per cent (anhydrous substance).

CHARACTERS

Appearance

White or almost white powder.

Solubility

Sparingly soluble in water, freely soluble in anhydrous ethanol, practically insoluble in heptane.

IDENTIFICATION

A. Specific optical rotation (see Tests).
B. Infrared absorption spectrophotometry (2.2.24).

Comparison capecitabine CRS.

TESTS

Specific optical rotation (2.2.7)

+ 96.0 to + 100.0 (anhydrous substance).

Dissolve 0.250 g in methanol R and dilute to 25.0 mL with the same solvent.

Related substances

Liquid chromatography (2.2.29). *Prepare the solutions immediately before use or store them at 2-8 °C.*

Solvent mixture acetonitrile R, methanol R, water R (5:35:60 *V/V/V*).

Test solution Dissolve 60.0 mg of the substance to be examined in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture.

Reference solution (a) Dissolve 60.0 mg of capecitabine CRS in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture.

Reference solution (b) Dilute 1.0 mL of the test solution to 100.0 mL with the solvent mixture. Dilute 1.0 mL of this solution to 20.0 mL with the solvent mixture.

Reference solution (c) Dissolve 3 mg of capecitabine impurity A CRS, 3 mg of capecitabine impurity B CRS and 5 mg of capecitabine impurity D CRS in 80 mL of the solvent mixture, sonicate until dissolution is complete and dilute to 100.0 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with 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);

— *temperature*: 40 °C.

Mobile phase:

— *mobile phase A*: acetonitrile R, methanol R, 0.1 per cent *V/V* solution of glacial acetic acid R (5:35:60 *V/V/V*);

— *mobile phase B*: acetonitrile R, 0.1 per cent *V/V* solution of glacial acetic acid R, methanol R (5:15:80 *V/V/V*);

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 5	100	0
5 - 20	100 → 49	0 → 51
20 - 30	49	51

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 250 nm.

Injection 10 µL of the test solution and reference solutions (b) and (c).

Identification of impurities Use the chromatogram obtained with reference solution (c) to identify the peaks due to impurities A, B and D.

Relative retention With reference to capecitabine (retention time = about 17 min): impurity A = about 0.18; impurity B = about 0.19; impurities D and E = about 0.95.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurities A and B; minimum 2.0 between the peaks due to impurity D and capecitabine.

Calculation of percentage contents:

— for each impurity, use the concentration of capecitabine in reference solution (b);

— *correction factor*: multiply the peak area of impurity B by 1.3.

Limits:

— *impurities A, B*: for each impurity, maximum 0.3 per cent;

— *sum of impurities D and E*: maximum 0.2 per cent;

— *unspecified impurities*: for each impurity, maximum 0.05 per cent;

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.03 per cent.

Water (*2.5.32*)

Maximum 0.3 per cent.

Inject 1.0 mL of a 0.200 g/mL solution of the substance to be examined in *methanol R*.

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 modification.

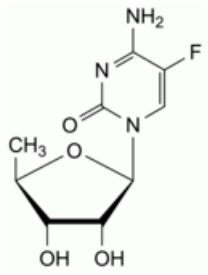
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{15}H_{22}FN_3O_6$ taking into account the assigned content of *capecitabine CRS*.

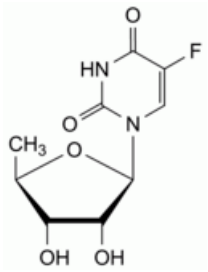
IMPURITIES

Specified impurities *A, B, D, E.*

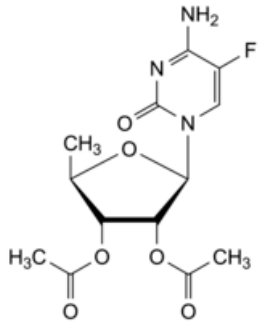
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



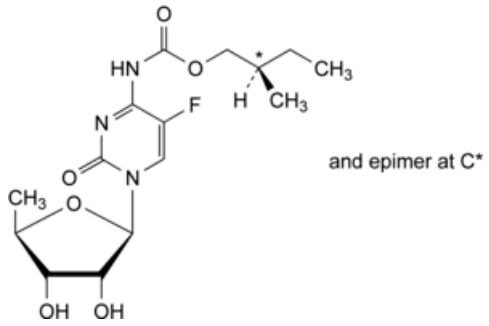
A. 4-amino-1-(5-deoxy-β-D-ribofuranosyl)-5-fluoropyrimidin-2(1*H*)-one (5'-deoxy-5-fluorocytidine),



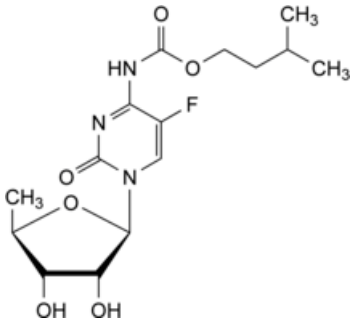
B. 1-(5-deoxy-β-D-ribofuranosyl)-5-fluoropyrimidine-2,4(1*H*,3*H*)-dione (5'-deoxy-5-fluorouridine),



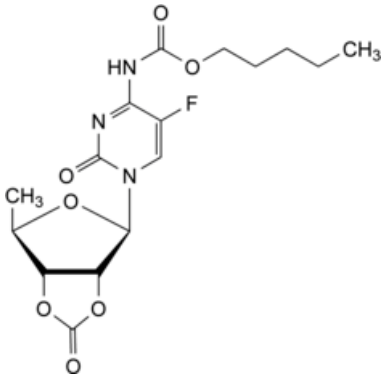
C. 1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-4-amino-5-fluoropyrimidin-2(1*H*)-one,



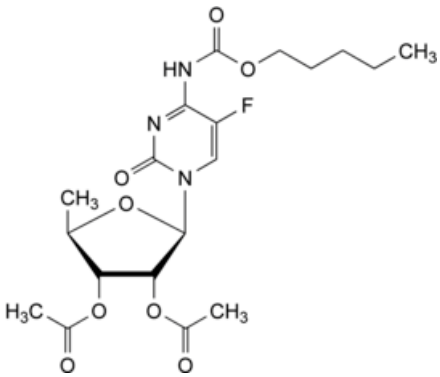
D. (2*RS*)-2-methylbutyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,



E. 3-methylbutyl [1-(5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,



F. pentyl [5-fluoro-1-[(3a*R*,4*R*,6*R*,6a*R*)-6-methyl-2-oxotetrahydrofuro[3,4-*d*][1,3]dioxol-4-yl]-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate,



G. pentyl [1-(2,3-di-*O*-acetyl-5-deoxy-β-D-ribofuranosyl)-5-fluoro-2-oxo-1,2-dihydropyrimidin-4-yl]carbamate.

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