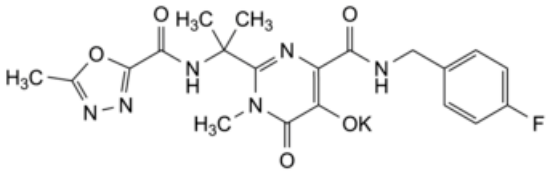
Edition: BP 2025 (Ph. Eur. 11.6 update)

Raltegravir Potassium

General Notices

(Ph. Eur. monograph 2887)



$C_{20}H_{20}FKN_6O_5$ 482.5 *871038-72-1*

Action and use

Antiviral (HIV).

Preparations

Raltegravir Chewable Tablets

Raltegravir Tablets

Ph Eur

DEFINITION

Potassium 4-[[(4-fluorophenyl)methyl]carbamoyl]-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidin-5-olate.

Content

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

CHARACTERS

Appearance

White or almost white powder.

Solubility

Soluble in water, very slightly soluble in ethanol (96 per cent), practically insoluble in heptane.

It shows polymorphism (*5.9*).

IDENTIFICATION

A. Infrared absorption spectrophotometry (2.2.24).

Comparison raltegravir potassium CRS.

If the spectra obtained in the solid state show differences, dissolve the substance to be examined and the reference substance separately in methanol R, evaporate to dryness and record new spectra using the residues.

B. It gives reaction (b) of potassium (2.3.1).

TESTS

Related substances

Liquid chromatography (2.2.29).

Solvent mixture acetonitrile R, water R (25:75 *V/V*).

Test solution Dissolve 25.0 mg of the substance to be examined in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 mL with the solvent mixture.

Reference solution (a) Dissolve 25.0 mg of raltegravir potassium CRS in 100 mL of the solvent mixture using sonication for 5 min. Add about 140 mL of the solvent mixture then dilute to 250.0 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 10.0 mL with the solvent mixture.

Reference solution (c) Dissolve 2 mg of raltegravir impurity E CRS in the solvent mixture and dilute to 20 mL with the solvent mixture. Dilute 1 mL of the solution to 50 mL with the test solution.

Reference solution (d) In order to prepare impurity C *in situ*, dissolve 20 mg of the substance to be examined in a 40 g/L solution of sodium hydroxide R and dilute to 10 mL with the same solvent. Stir the solution for 30 min. To 5 mL of the solution add 5 mL of a 103 g/L solution of hydrochloric acid R and dilute to 50 mL with the solvent mixture.

Reference solution (e) Dissolve 5 mg of raltegravir for peak identification CRS (containing impurities F and G) in 20 mL of the solvent mixture using sonication for 5 min. Add about 25 mL of the solvent mixture then dilute to 50 mL with the solvent mixture.

Column:

— *size*: *l* = 0.15 m, Ø = 4.6 mm;

— *stationary phase*: phenylsilyl silica gel for chromatography R (3.5 µm);

— *temperature*: 15 °C.

Mobile phase:

— *mobile phase A*: 0.1 per cent *V/V* solution of phosphoric acid R;

— *mobile phase B*: acetonitrile for chromatography R;

Time (min)	Mobile phase A (per cent *V/V*)	Mobile phase B (per cent *V/V*)
0 - 2	75	25
2 - 5	75 → 60	25 → 40
5 - 10	60 → 55	40 → 45
10 - 19	55 → 10	45 → 90
19 - 22	10 → 5	90 → 95

Flow rate 1.0 mL/min.

Detection Spectrophotometer at 220 nm.

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

Identification of impurities Use the chromatogram obtained with reference solution (d) to identify the peak due to impurity C; use the chromatogram obtained with reference solution (c) to identify the peak due to impurity E; use the chromatogram supplied with *raltegravir for peak identification CRS* and the chromatogram obtained with reference solution (e) to identify the peaks due to impurities F and G.

Relative retention With reference to raltegravir (retention time = about 10 min): impurity C = about 0.7; impurity E = about 0.95; impurity G = about 1.1; impurity F = about 1.15.

System suitability Reference solution (c):

— *resolution*: minimum 1.5 between the peaks due to impurity E and raltegravir.

Calculation of percentage contents:

— for each impurity, use the concentration of raltegravir potassium in reference solution (b).

Limits:

— *impurity C*: maximum 0.2 per cent;

— *impurities E, F, G*: for each impurity, maximum 0.15 per cent;

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

— *total*: maximum 0.5 per cent;

— *reporting threshold*: 0.05 per cent.

Water (*2.5.12*)

Maximum 0.6 per cent, determined on 0.500 g. Use as the solvent a mixture of equal volumes of *methanol R* and *formamide R*.

ASSAY

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

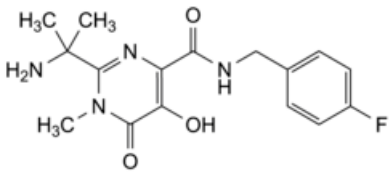
Injection Test solution and reference solution (a).

Calculate the percentage content of $C_{20}H_{20}FKN_6O_5$ taking into account the assigned content of *raltegravir potassium CRS*.

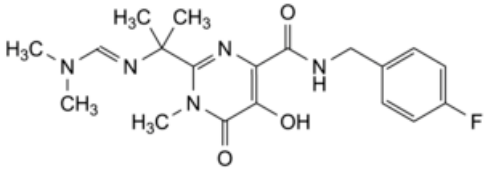
IMPURITIES

Specified impurities *C, E, F, G*.

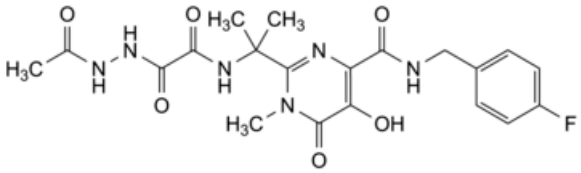
Other detectable impurities (the following substances would, if present at a sufficient level, be detected by one or other of the tests in the monograph. They are limited by the general acceptance criterion for other/unspecified impurities and/or by the general monograph Substances for pharmaceutical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



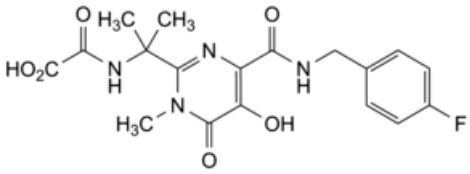
A. 2-(2-aminopropan-2-yl)-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



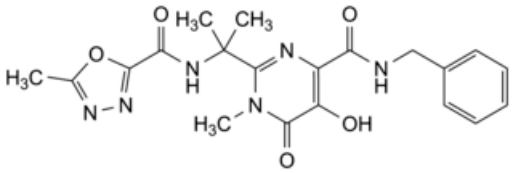
B. 2-[2-[(*E*)-[(dimethylamino)methylidene]amino]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



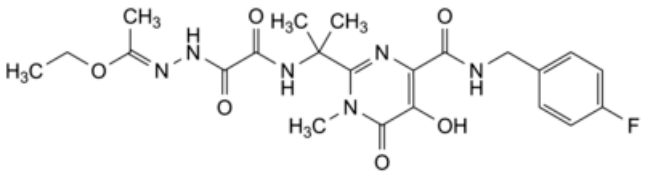
C. 2-[2-[2-(2-acetylhydrazin-1-yl)-2-oxoacetamido]propan-2-yl]-*N*-[(4-fluorophenyl)methyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



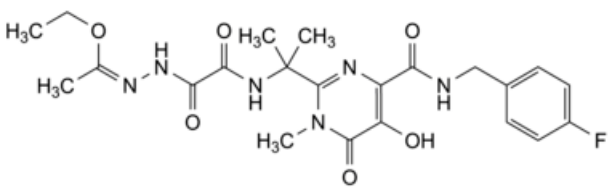
D. [[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]amino]oxoacetic acid,



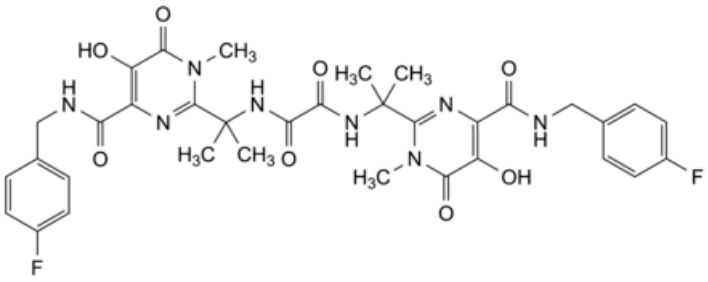
E. *N*-benzyl-5-hydroxy-1-methyl-2-[2-(5-methyl-1,3,4-oxadiazole-2-carboxamido)propan-2-yl]-6-oxo-1,6-dihydropyrimidine-4-carboxamide,



F. ethyl (1*E*)-*N*-[[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamoyl]ethanehydrazonate,



G. ethyl (1*Z*)-*N*-[[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamoyl]ethanehydrazonate,



H. N^1,N^2-bis[2-[4-[[(4-fluorophenyl)methyl]carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl]oxamide.

Ph Eur