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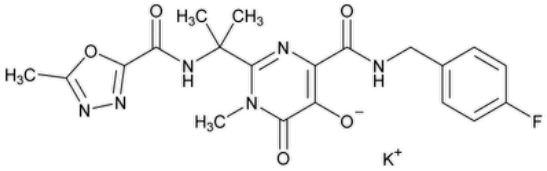
Raltegravir Potassium



$C_{20}H_{20}FKN_6O_5$ 482.51

4-Pyrimidinecarboxamide, *N*-[(4-fluorophenyl)methyl]-1,6-dihydro-5-hydroxy-1-methyl-2-[1-methyl-1-[[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino]ethyl]-6-oxo-, monopotassium salt;
Potassium 4-[(4-fluorobenzyl)carbamoyl]-1-methyl-2-(1-methyl-1-{[(5-methyl-1,3,4-oxadiazol-2-yl)carbonyl]amino}ethyl)-6-oxo-1,6-dihydropyrimidin-5-olate CAS RN®: 871038-72-1.

DEFINITION

Raltegravir Potassium contains NLT 98.0% and NMT 102.0% of raltegravir potassium ($C_{20}H_{20}FKN_6O_5$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

Change to read:

• **A.** ▲**Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A, 197K, or 197M▲ (CN 1-May-2020)

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

• **B.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

• **C.**

Solution A: 100 g/L of sodium cobaltinitrite in water

Sample solution: 40 mg/mL of Raltegravir Potassium in water

Analysis: Combine 1 mL of *Sample solution* with 1 mL of dilute acetic acid and 1 mL of *Solution A*.

Acceptance criteria: A yellow or orange yellow precipitate is formed immediately.

ASSAY

• **Procedure**

Diluent: Acetonitrile and water (25:75)

Solution A: Phosphoric acid and water (1:1000)

Solution B: Acetonitrile

Mobile phase: See *Table 1*. Return to original conditions and re-equilibrate the system.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
2	75	25
5	60	40

Time (min)	Solution A (%)	Solution B (%)
10	55	45
19	10	90
22	5	95

Standard solution: 0.1 mg/mL of USP Raltegravir Potassium RS in *Diluent* prepared as follows. Transfer a suitable amount of USP Raltegravir Potassium RS to a suitable volumetric flask and add about 40% of the flask volume of *Diluent*. Sonicate for 5 min, add the *Diluent* to about 90% of the final volume, and allow to stand for 30 min. Dilute with *Diluent* to volume.

Sample solution: 0.1 mg/mL of Raltegravir Potassium in *Diluent* prepared as follows. Transfer a suitable amount of the sample to a suitable volumetric flask and add about 40% of the flask volume of *Diluent*. Sonicate for 5 min, add the *Diluent* to about 90% of the final volume, and allow to stand for 30 min. Dilute with *Diluent* to volume.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

Mode: LC

Detector: UV 220 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L11

Column temperature: 15°

Flow rate: 1 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of raltegravir potassium ($C_{20}H_{20}FKN_6O_5$) in the portion of Raltegravir Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of raltegravir from the *Sample solution*

r_S = peak response of raltegravir from the *Standard solution*

C_S = concentration of USP Raltegravir Potassium RS in the *Standard solution* (mg/mL)

C_U = concentration of Raltegravir Potassium in the *Sample solution* (mg/mL)

Acceptance criteria: 98.0%–102.0% on the anhydrous and solvent-free basis

IMPURITIES

• **Organic Impurities**

Diluent, Solution A, Solution B, Mobile phase, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

Peak identification solution: Prepare a solution containing 2 mg/mL of USP Raltegravir Potassium RS in 1 N sodium hydroxide solution. Stir the solution for 2 h at room temperature. Transfer 5 mL of this solution to a 50-mL volumetric flask and add 5 mL of 1 N hydrochloric acid. Dilute with *Diluent* to volume. [Note—In situ degradation generates raltegravir amine and raltegravir oxalylacetohydrazide analog.]

System suitability solution: 0.1 mg/mL of USP Raltegravir Potassium RS and 0.2 µg/mL of USP Raltegravir Related Compound E RS in *Diluent*

Standard stock solution: Use the *Standard solution* prepared in the *Assay*.

Standard solution: 0.1 µg/mL of USP Raltegravir Potassium RS in *Diluent* from *Standard stock solution*

System suitability

Sample: *System suitability solution*

[Note—See *Table 2* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between raltegravir related compound E and raltegravir

Analysis

Samples: *Sample solution*, *Peak identification solution*, and *Standard solution*

Calculate the percentage of any individual impurity in the portion of Raltegravir Potassium taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = peak response of each individual impurity from the *Sample solution*

r_S = peak response of raltegravir from the *Standard solution*

C_S = concentration of USP Raltegravir Potassium RS in the *Standard solution* (mg/mL)

C_U = concentration of Raltegravir Potassium in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. Reporting threshold is 0.05%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Raltegravir amine[a]	0.43	0.15
Raltegravir formididyl analog[b]	0.60	0.15
Raltegravir oxalylacetohydrazide analog[c]	0.72	0.20
Raltegravir related compound E	0.94	0.15
Raltegravir	1.0	—
Raltegravir *E*-ethoxyacethydrazone analog[d]	1.1	0.20
Raltegravir *Z*-ethoxyacethydrazone analog[e]	1.2	0.15
Any individual, unspecified impurity	—	0.10
Total impurities	—	0.7

[a] 2-(2-Aminopropan-2-yl)-*N*-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide.

[b] (*E*)-2-(2-{[(Dimethylamino)methylidene]amino}propan-2-yl)-*N*-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide.

[c] 2-{2-[2-(2-Acetylhydrazinyl)-2-oxoacetamido]propan-2-yl}-*N*-(4-fluorobenzyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidine-4-carboxamide.

[d] Ethyl (*E*)-*N*-{2-[(2-{4-[(4-fluorobenzyl)carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl}propan-2-yl)amino]-2-oxoacetyl}acetohydrazonate.

[e] Ethyl (*Z*)-*N*-{2-[(2-{4-[(4-fluorobenzyl)carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl}propan-2-yl)amino]-2-oxoacetyl}acetohydrazonate.

SPECIFIC TESTS

• **Water Determination ⟨921⟩**

Sample: 0.5 g

[Note—A mixture of equal volumes of methanol and formamide is suitable as solvent. Hydranal-Composite 2 is suitable as reagent.]

Acceptance criteria: NMT 0.6%

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.
- **USP Reference Standards** ⟨11⟩

USP Raltegravir Potassium RS

USP Raltegravir Related Compound E RS

N-{2-[4-(Benzylcarbamoyl)-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl]propan-2-yl}-5-methyl-1,3,4-oxadiazole-2-carboxamide.

$C_{20}H_{22}N_6O_5$ 426.43

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
RALTEGRAVIR POTASSIUM	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

Chromatographic Database Information: Chromatographic Database

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