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Raltegravir Tablets

DEFINITION

Change to read:

Raltegravir Tablets contain an amount of Raltegravir Potassium equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of raltegravir ($▲C_{20}H_{21}FN_6O_5$).▲ (ERR 1-May-2020)

IDENTIFICATION

Change to read:

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

Sample: Grind a Tablet, and use a suitable amount of the powdered Tablet to prepare a specimen.

Acceptance criteria: The spectrum obtained from the *Sample* shows bands at approximately 1633, 1515, 1188, 810, and 728 cm^{-1}, similar to the spectrum from the Standard similarly obtained. [Note—Peak positions may vary slightly between instruments (within ±10 cm^{-1}). Other peaks may be present in the spectra that do not appear in this list.]

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

ASSAY

Change to read:

• **Procedure**

Buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (29:71)

Solution A: Acetonitrile and water (50:50)

Diluent: Acetonitrile and water (30:70)

Standard solution: 0.22 mg/mL of USP Raltegravir Potassium RS in *Diluent*

Sample stock solution: Nominally equivalent to 8 mg/mL of raltegravir from Tablets prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask and dilute with *Solution A* to volume. Stir the flask vigorously for 1 h. Centrifuge a portion of the solution and use the supernatant for *Sample solution* preparation.

Sample solution: Nominally 0.2 mg/mL of raltegravir in *Diluent* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 15-cm; 5-µm packing *L1*

Column temperature: 40°

Flow rate: 2 mL/min

Injection volume: 30 µL

Run time: NLT 1.5 times the retention time of raltegravir

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of raltegravir ($C_{20}H_{20}FN_6O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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 = nominal concentration of raltegravir in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of raltegravir, ▲444.42▲ (ERR 1-May-2020)

M_{r2} = molecular weight of raltegravir potassium, 482.51

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

• **Dissolution** ⟨711⟩

Medium: *Water*; 900 mL, deaerated

Apparatus 2: 100 rpm with sinker

Times: 15 and 60 min

Buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 3.0.

Mobile phase: Acetonitrile and *Buffer* (38:62)

Diluent: Acetonitrile and water (20:80)

Standard solution: 0.48 mg/mL of USP Raltegravir Potassium RS in *Diluent*. Sonicate, if necessary, to dissolve prior to final dilution.

Sample solution: Pass a portion of the solution under test through a suitable filter.

Chromatographic system

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

Mode: LC

Detector: UV 303 nm

Column: 4.6-mm × 10-cm; packing L1

Column temperature: 40°

Flow rate: 5 mL/min

Injection volume: 10 µL

Run time: 1 min

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 3.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of raltegravir ($C_{20}H_{20}FN_6O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times (1/L) \times V \times D \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

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

L = label claim (mg/Tablet)

V = volume of *Medium*, 900 mL

D = dilution factor for the *Sample solution*, if needed

M_{r1} = molecular weight of raltegravir, ▲444.42▲ (ERR 1-May-2020)

M_{r2} = molecular weight of raltegravir potassium, 482.51

Tolerances: 15%–45% of the labeled amount of raltegravir is dissolved in 15 min, and NLT 70% (*Q*) of the labeled amount of raltegravir is dissolved in 60 min.

• **Uniformity of Dosage Units ⟨905⟩:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**

Buffer, Mobile phase, Solution A, Diluent, 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 the raltegravir amine and raltegravir oxalylacetohydrazide analog peaks along with a small peak for raltegravir oxalyl analog impurity.]

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

System suitability

Samples: *System suitability solution* and *Standard solution*

[Note—See *Table 1* for relative retention times.]

Suitability requirements

Resolution: NLT 1.5 between raltegravir related compound E and raltegravir, *System suitability solution*

Relative standard deviation: NMT 10.0%, *Standard solution*

Analysis

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

Calculate the percentage of any individual impurity in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times (1/F) \times 100$$

r_U = peak response of any 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 = nominal concentration of raltegravir in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of raltegravir, ▲444.42▲ (ERR 1-May-2020)

M_{r2} = molecular weight of raltegravir potassium, 482.51

F = relative response factor (see *Table 1*)

Acceptance criteria: See *Table 1*. Reporting threshold is 0.1%.

Table 1

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Raltegravir amine[a]	0.14	1.0	—[b]
Raltegravir formididyl analog[c]	0.29	1.0	—[b]
Raltegravir oxalyl analog[d]	0.33	1.0	0.3
Raltegravir oxalylacetohydrazide analog[e]	0.48	0.75	0.5

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Raltegravir related compound E	0.83	1.0	—[b]
Raltegravir	1.0	—	—
Any individual unspecified impurity	—	1.0	0.2
Total impurities	—	—	0.8

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

[b] This is a process impurity controlled in the drug substance and not monitored in the drug product.

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

[d] 2-[(2-{4-[(4-Fluorobenzyl)carbamoyl]-5-hydroxy-1-methyl-6-oxo-1,6-dihydropyrimidin-2-yl}propan-2-yl)amino]-2-oxoacetic acid.

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

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 TABLETS	Documentary Standards Support	SM12020 Small Molecules 1
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM12020 Small Molecules 1

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