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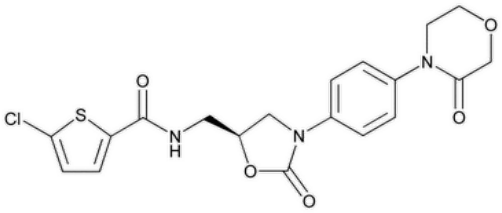
Add the following:

▲Rivaroxaban



$C_{19}H_{18}ClN_3O_5S$ 435.88

2-Thiophenecarboxamide, 5-chloro-*N*-[[(5*S*)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-5-oxazolidinyl]methyl]-;

5-Chloro-*N*-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide CAS RN®: 366789-02-8; UNII: 9NDF7JZ4M3.

DEFINITION

Rivaroxaban contains NLT 98.0% and NMT 102.0% of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$), calculated on the anhydrous basis.

IDENTIFICATION

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197A or 197K

• **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

• **Procedure**

Solution A: Dissolve 1.36 g of potassium dihydrogenphosphate, 1 g of sodium hexane sulfonate, and 200 µL of phosphoric acid in water. Dilute with water to 1 L.

Solution B: Dissolve 1.36 g of potassium dihydrogenphosphate and 200 µL of phosphoric acid in water. Dilute with water to 1 L.

Diluent: Acetonitrile and *Solution B* (40:60)

Solution C: Methanol and *Solution A* (5:95)

Solution D: Acetonitrile

Mobile phase: See *Table 1*. NLT 7 min of column equilibration with the initial mobile phase conditions is recommended between injections.

Table 1

Time (min)	Solution C (%)	Solution D (%)
0	98	2
2	98	2
8	84	16
25	64	36
37	20	80

Standard solution: 0.5 mg/mL of USP Rivaroxaban RS in *Diluent*

Sample solution: 0.5 mg/mL of Rivaroxaban in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 3.0-mm × 15-cm; 3.5-µm packing L1

Column temperature: 60°

Flow rate: 1 mL/min

Injection volume: 3 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 0.73%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) in the portion of Rivaroxaban taken:

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

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

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

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

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

Acceptance criteria: 98.0%–102.0% on the anhydrous basis

IMPURITIES

- **Residue on Ignition ⟨281⟩:** NMT 0.1%
- **Organic Impurities**

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

System suitability solution: 0.5 mg/mL of USP Rivaroxaban RS and 0.5 µg/mL each of USP Rivaroxaban Related Compound B RS, USP Rivaroxaban Related Compound D RS, USP Rivaroxaban Related Compound G RS, and USP Rivaroxaban Related Compound J RS in *Diluent*

Standard solution: 0.5 µg/mL of USP Rivaroxaban RS in *Diluent*

Sensitivity solution: 0.25 µg/mL of USP Rivaroxaban RS in *Diluent* from the *Standard solution*

System suitability

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

Suitability requirements

Resolution: NLT 8.0 between rivaroxaban related compound G and rivaroxaban, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Samples: *Sample solution* and *Standard solution*

Calculate the percentage of each individual impurity in the portion of Rivaroxaban 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 rivaroxaban from the *Standard solution*

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

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

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

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Rivaroxaban related compound B	0.34	0.15
Rivaroxaban related compound D	0.57	0.15
Rivaroxaban related compound G[a]	0.87	0.10
Rivaroxaban	1.00	—
Rivaroxaban related compound J	1.82	0.15
Any unspecified impurity	—	0.10
Total impurities	—	0.50

[a] This impurity is included for establishing the *Resolution* requirement in *System suitability*. It is controlled as an unspecified impurity.

• **Enantiomeric Purity**

Mobile phase: Acetonitrile

System suitability solution: 0.5 mg/mL of USP Rivaroxaban RS and 0.015 mg/mL of USP Rivaroxaban R-Enantiomer RS in acetonitrile

Sensitivity solution: 0.25 µg/mL of USP Rivaroxaban R-Enantiomer RS in acetonitrile

Standard solution: 0.5 µg/mL of USP Rivaroxaban RS in acetonitrile

Sample solution: 0.5 mg/mL of Rivaroxaban in acetonitrile

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 25-cm; 5-µm packing L119

Temperatures

Autosampler: 12°

Column: 30°

Flow rate: 0.7 mL/min

Injection volume: 20 µL

Run time: NLT 2.5 times the retention time of rivaroxaban

System suitability

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

[Note—The relative retention times for the rivaroxaban *R*-enantiomer and rivaroxaban are about 0.8 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between the rivaroxaban *R*-enantiomer and rivaroxaban, *System suitability solution*

Relative standard deviation: NMT 5.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*

Analysis

Sample: *Sample solution*

Calculate the percentage of enantiomeric excess in the portion of Rivaroxaban taken:

$$\text{Result} = (r_1 - r_2)/(r_1 + r_2) \times 100$$

r_1 = peak response of rivaroxaban from the *Sample solution*

r_2 = peak response of the rivaroxaban *R*-enantiomer from the *Sample solution*

Acceptance criteria: NLT 99.0%

SPECIFIC TESTS

• **Water Determination** ⟨921⟩, *Method I, Method Ic*: NMT 1.0%

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight, light-resistant containers at controlled room temperature. Keep away from heat and moisture.

• **USP Reference Standards** ⟨11⟩

USP Rivaroxaban RS

USP Rivaroxaban R-Enantiomer RS

(*R*)-5-Chloro-*N*-({2-oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)thiophene-2-carboxamide.

$C_{19}H_{18}ClN_3O_5S$ 435.88

USP Rivaroxaban Related Compound B RS

(*S*)-*N*-({2-Oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)acetamide.

$C_{16}H_{19}N_3O_5$ 333.34

USP Rivaroxaban Related Compound D RS

1,3-Bis({(*S*)-2-oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)urea.

$C_{29}H_{32}N_6O_9$ 608.61

USP Rivaroxaban Related Compound G RS

(*S*)-2-({2-Oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)isoindoline-1,3-dione.

$C_{22}H_{19}N_3O_6$ 421.41

USP Rivaroxaban Related Compound J RS

5-Chloro-*N*-(4-{(*S*)-5-[(5-chlorothiophene-2-carboxamido)methyl]-2-oxooxazolidin-3-yl}phenyl)-*N*-(2-{2-oxo-2-[({(*S*)-2-oxo-3-[4-(3-oxomorpholino)phenyl]oxazolidin-5-yl}methyl)amino]ethoxy}ethyl)thiophene-2-carboxamide.

$C_{38}H_{36}Cl_2N_6O_{10}S_2$ 871.76▲ (USP 1-Dec-2022)

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

Topic/Question	Contact	Expert Committee
RIVAROXABAN	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

Most Recently Appeared In:
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