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Add the following:

▲Riociguat Tablets

DEFINITION
Riociguat Tablets contain NLT 95.0% and NMT 105.0% of the labeled amount of riociguat ($C_{20}H_{19}FN_8O_2$).

IDENTIFICATION
• **A.** The UV spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.
• **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**
[Note—Protect all solutions containing riociguat from light.]

Buffer: Phosphoric acid in water (5.5: 1000). Adjust with phosphoric acid to a pH of 1.6.

Mobile phase: Acetonitrile and *Buffer* (23:77)

Diluent: Acetonitrile and *Buffer* (20:80)

Standard solution: 0.1 mg/mL of USP Riociguat RS in *Diluent*. Sonicate to dissolve as necessary.

System suitability solution: 0.1 mg/mL of USP Riociguat System Suitability Mixture II RS in *Diluent*. Sonicate to dissolve as necessary.

Sample solution: Nominally 0.1 mg/mL of riociguat in *Diluent* prepared as follows. Transfer NLT 5 Tablets to a suitable volumetric flask and add 70% of the flask volume of the *Diluent*. Shake for 15 min on a shaker to completely disintegrate the Tablets. Dilute with *Diluent* to volume. (Alternatively, the flask can be sonicated for 30 min to disintegrate the Tablets, and then dilute with *Diluent* to volume.) Centrifuge a portion of the resulting solution and use the clear supernatant.

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

Mode: LC

Detector: UV 210 nm. For *Identification A*, use a diode array detector in the range of 210–400 nm.

Column: 4.6-mm × 10-cm; 3.5-µm packing L1

Column temperature: 40°

Flow rate: 2.0 mL/min

Injection volume: 5 µL

Run time: NLT 4 times the retention time of riociguat

System suitability

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

[Note—See *Table 1* for the relative retention times. The relative retention times for riociguat related compound A, riociguat, and riociguat related compound C are 0.65, 1.0, and 2.4, respectively.]

Suitability requirements

Resolution: NLT 5.0 between riociguat related compound A and riociguat, *System suitability solution*

Tailing factor: 1.0–1.5, *Standard solution*

Relative standard deviation: NMT 1.0% from 6 replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of riociguat ($C_{20}H_{19}FN_8O_2$) in the portion of Tablets taken:

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

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

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

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

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

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

• **Dissolution ⟨711⟩**

Medium: pH 6.8 phosphate buffer containing 0.1% sodium lauryl sulfate, prepared as follows. Dissolve 2.75 g of sodium phosphate, dibasic, dihydrate, 0.48 g of citric acid, and 1.0 g of sodium lauryl sulfate in 1 L of water and adjust with 0.1 N sodium hydroxide solution or phosphoric acid to a pH of 6.8; 900 mL.

Apparatus 2: 75 rpm

Time: 15 min

Buffer: Dissolve 1.54 g/L of ammonium acetate in water and adjust with glacial acetic acid to a pH of 4.0.

Mobile phase: Acetonitrile and *Buffer* (45:55)

Standard stock solution: 0.028 mg/mL of USP Riociguat RS in methanol

Standard solution: (*L*/900) mg/mL of USP Riociguat RS in *Medium* from *Standard stock solution*, where *L* is the label claim of riociguat in mg/Tablet

Sample solution: A filtered portion of the solution under test

Chromatographic system

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

Mode: LC

Detector: UV 326 nm

Column: 4.6-mm × 6-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 2.3 mL/min

Injection volume: 100 µL

Run time: NLT 1.9 times the retention time of riociguat

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.5% from 6 replicate injections

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of riociguat ($C_{20}H_{19}FN_8O_2$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of riociguat is dissolved.

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

IMPURITIES

• **Organic Impurities**

[Note—Protect all solutions containing riociguat from light.]

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

Standard solution: 0.0001 mg/mL of USP Riociguat RS in *Diluent*. Sonicate to dissolve as needed.

System suitability

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

[NOTE—See *Table 1* for the relative retention times. The relative retention times for riociguat related compound A, riociguat, and riociguat related compound C are 0.65, 1.0, and 2.4, respectively.]

Suitability requirements

Resolution: NLT 5.0 between riociguat related compound A and riociguat, *System suitability solution*

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual degradation product in the portion of Tablets taken:

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

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

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

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

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

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

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Riociguat	1.0	—
Any unspecified degradation product	—	0.2
Total degradation products	—	1.0

ADDITIONAL REQUIREMENTS

• **PACKAGING AND STORAGE:** Preserve in tight containers. Store at controlled room temperature.

• **USP REFERENCE STANDARDS** ⟨11⟩

USP Riociguat RS

USP Riociguat System Suitability Mixture II RS

This is a mixture containing (approximately 0.2% of riociguat related compound A and 0.5% of riociguat related compound C):
Riociguat.
Riociguat related compound A: Methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl}carbamate; also known as Nelociguat.
$C_{19}H_{17}FN_8O_2$ 408.40
Riociguat related compound C: Methyl {4-amino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-6-(methylamino)pyrimidin-5-yl}methylcarbamate. $C_{21}H_{21}FN_8O_2$ 436.45▲ (USP 1-Aug-2022)

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

Topic/Question	Contact	Expert Committee
RIOCIGUAT TABLETS	Documentary Standards Support	SM52020 Small Molecules 5
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM52020 Small Molecules 5

Chromatographic Database Information: Chromatographic Database

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