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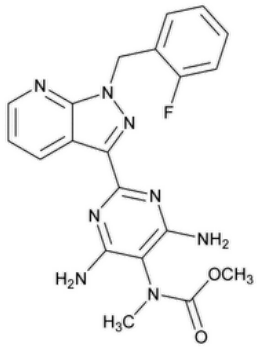
Add the following:

▲Riociguat



$C_{20}H_{19}FN_8O_2$ 422.42

Carbamic acid, *N*-[4,6-diamino-2-[1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]-5-pyrimidinyl]-*N*-methyl-, methyl ester;
Methyl *N*-(4,6-diamino-2-{1-[(2-fluorophenyl)methyl]-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl}pyrimidin-5-yl)-*N*-methylcarbamate;
Methyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl}(methyl)carbamate CAS RN®: 625115-55-1; UNII: RU3FE2Y4XI.

DEFINITION

Riociguat contains NLT 98.0% and NMT 102.0% of riociguat ($C_{20}H_{19}FN_8O_2$), calculated on the solvent-free 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**

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

Solution A: Perchloric acid in water (4:1000)

Solution B: Acetonitrile

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

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	75	25
2	75	25
27	65	35
42	32	68
43	10	90

Time (min)	Solution A (%)	Solution B (%)
52	10	90

Diluent: *Solution A* and *Solution B* (20:80)

System suitability solution: 0.4 mg/mL of USP Riociguat System Suitability Mixture RS in *Diluent*. Sonicate to dissolve as needed.

Standard solution: 0.4 mg/mL of USP Riociguat RS in *Diluent*. Sonicate to dissolve as needed.

Sample solution: 0.4 mg/mL of Riociguat in *Diluent*. Sonicate to dissolve as needed.

Chromatographic system

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

Mode: LC

Detector: UV 210 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 15°

Column: 40°

Flow rate: 1.0 mL/min

Injection volume: 5 µL

System suitability

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

[NOTE—See *Table 2* for relative retention times. The relative retention times for riociguat related compound B and riociguat are 0.97 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between riociguat related compound B and riociguat, *System suitability solution*

Tailing factor: 1.0–1.5, *Standard solution*

Relative standard deviation: NMT 0.85% from 6 replicate injections, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of riociguat ($C_{20}H_{19}FN_8O_2$) in the portion of Riociguat 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 = concentration of Riociguat in the *Sample solution* (mg/mL)

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

IMPURITIES

• **RESIDUE ON IGNITION ⟨281⟩:** NMT 0.1%

• **ORGANIC IMPURITIES**

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

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

Standard solution: 0.0004 mg/mL of USP Riociguat RS in *Diluent*. Sonicate to dissolve as needed.

Sensitivity solution: 0.0002 mg/mL of USP Riociguat RS in *Diluent* from *Standard solution*

System suitability

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

[NOTE—See *Table 2* for relative retention times. The relative retention times for riociguat related compound B and riociguat are 0.97 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.5 between riociguat related compound B and riociguat, *System suitability solution*

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

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of each individual impurity in the portion of Riociguat 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 riociguat from the *Standard solution*

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

C_U = concentration of Riociguat 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 (%)
Riociguat related compound A[a]	0.78	0.15
Riociguat	1.0	—
Riociguat related compound C	1.4	0.20
Riociguat related compound D[b]	1.5	0.15
Any individual unspecified impurity	—	0.10
Total impurities	—	0.7

[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.

[b] Isopropyl {4,6-diamino-2-[1-(2-fluorobenzyl)-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl]pyrimidin-5-yl}(methyl)carbamate.

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 RS

This is a mixture containing the following components:

Riociguat.

Riociguat related compound B: Methyl {4,6-diamino-2-(1-benzyl-1*H*-pyrazolo[3,4-*b*]pyridin-3-yl)pyrimidin-5-yl}(methyl)carbamate.

$C_{20}H_{20}N_8O_2$ 404.43

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}(methyl)carbamate.

$C_{21}H_{21}FN_8O_2$ 436.45▲ (USP 1-Dec-2021)

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

Topic/Question	Contact	Expert Committee
RIOCIGUAT	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

Most Recently Appeared In:
Pharmacopeial Forum: Volume No. 46(3)

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