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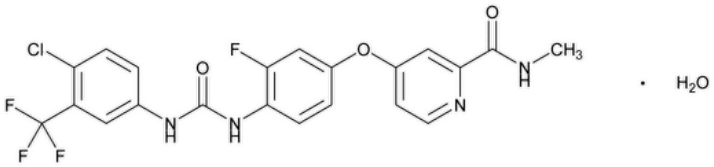
Add the following:

▲Regorafenib



$C_{21}H_{15}ClF_4N_4O_3 \cdot H_2O$ 500.83

2-Pyridinecarboxamide, 4-[4-[[[[4-chloro-3-(trifluoromethyl)phenyl]amino]carbonyl]amino]-3-fluorophenoxy]-*N*-methyl-, monohydrate;

4-[4-({[4-Chloro-3-(trifluoromethyl)phenyl]carbamoyl}amino)-3-fluorophenoxy]-*N*-methylpyridine-2-carboxamide monohydrate CAS RN®: 1019206-88-2.

Anhydrous

$C_{21}H_{15}ClF_4N_4O_3$ 482.82 CAS RN®: 755037-03-7.

DEFINITION

Regorafenib contains NLT 97.5% and NMT 101.5% of regorafenib ($C_{21}H_{15}ClF_4N_4O_3$), calculated on the anhydrous and solvent-free basis.

IDENTIFICATION

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

• **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**

Store the solutions containing regorafenib at 2°–8° and protect from light.

Solution A: 0.1% (v/v) trifluoroacetic acid in water

Solution B: Acetonitrile and *Solution A* (3:97)

Mobile phase: See *Table 1*. Return to original conditions, and equilibrate the system for at least 5 min.

Table 1

Time (min)	Solution B (%)	Acetonitrile (%)
0	100	0
2	100	0
15	78	22
25	60	40
33	36	64
37	36	64

Standard solution: 0.45 mg/mL of USP Regorafenib RS in methanol

Sample solution: 0.45 mg/mL of Regorafenib in methanol

Chromatographic system

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

Mode: LC

Detector: UV 232 nm

Column: 2.1-mm × 15-cm; 3.5-µm packing L11

Temperatures

Autosampler: 8°

Column: 63°

Flow rate: 0.9 mL/min

Injection volume: 5 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 regorafenib ($C_{21}H_{15}ClF_4N_4O_3$) in the portion of Regorafenib taken:

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

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

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

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

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

Acceptance criteria: 97.5%–101.5% on the anhydrous and solvent-free basis

IMPURITIES

• **Organic Impurities**

Store the solutions containing regorafenib at 2°–8° and protect from light.

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

Standard stock solution: 1.5 mg/mL of USP Regorafenib RS in methanol

Standard solution: 1.5 µg/mL of USP Regorafenib RS in methanol, from *Standard stock solution*

System suitability solution: 4.0 µg/mL of USP Sorafenib Tosylate RS in *Standard stock solution*

Sensitivity solution: 0.75 µg/mL of USP Regorafenib RS in methanol, from *Standard solution*

Sample solution: 1.5 mg/mL of Regorafenib in methanol

System suitability

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

[Note—The relative retention times for sorafenib and regorafenib are 0.9 and 1.0, respectively.]

Suitability requirements

Resolution: NLT 3.0 between the sorafenib and regorafenib peaks, *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 impurity in the portion of Regorafenib taken:

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

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

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

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

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

F = relative response factor (see *Table 2*)

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Regorafenib dipicolinamide analog[a]	0.43	2.0	0.15
Regorafenib diarylurea analog[b]	0.76	1.7	0.25
Regorafenib	1.00	—	—
4-Arylurea regorafenib analog[c]	1.27	0.95	0.15
Any individual unspecified impurity	—	1.0	0.10
Total impurities	—	—	1.0

[a] 4-(3-Fluoro-4-{[2-(methylcarbamoyl)pyridin-4-yl]amino}phenoxy)-*N*-methylpicolinamide.

[b] *N*,*N*′-Bis{4-[2-(*N*-methylcarbamoyl)-4-pyridyloxy]-2-fluorophenyl}urea.

[c] 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl]ureido}-3-(4-{3-[4-chloro-3-(trifluoromethyl)phenyl]ureido}-3-fluorophenoxy)phenoxy)-*N*-methylpicolinamide.

• **Limit of Regorafenib Related Compound A**

Store the solutions containing regorafenib or regorafenib related compound A at 2°–8° and protect from light.

Solution A: Dissolve 1.5 g of potassium phosphate, monobasic and 0.5 g of potassium phosphate, dibasic in 1 L of water.

Solution B: *Solution A* and acetonitrile (92:8)

Mobile phase: See *Table 3*. Return to original conditions, and equilibrate the system for at least 10 min.

Table 3

Time (min)	Solution B (%)	Acetonitrile (%)
0	100	0
2	100	0
17	22	78

Standard solution: 0.075 mg/mL of USP Regorafenib Related Compound A RS in tetrahydrofuran

Sample solution: 50.0 mg/mL of Regorafenib in tetrahydrofuran

Chromatographic system

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

Mode: LC

Detector: UV 228 nm

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

Temperatures

Autosampler: 2°–8°

Column: 50°

Flow rate: 1.0 mL/min

Injection volume: 3 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 10.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of regorafenib related compound A in the portion of Regorafenib taken:

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

r_U = peak response of regorafenib related compound A from the *Sample solution*

r_S = peak response of regorafenib related compound A from the *Standard solution*

C_S = concentration of USP Regorafenib Related Compound A RS in the *Standard solution* (mg/mL)

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

Acceptance criteria: NMT 0.15%

SPECIFIC TESTS

• **Water Determination ⟨921⟩, *Method I, Method Ic***

Sample: 50 mg

Test preparation: Evaporation technique

Temperature: 150°

Heating time: 3 min

Carrier gas: Nitrogen

Flow rate: 70 mL/min

Acceptance criteria: 3.2%–4.0% for monohydrate form

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers, and protect from light. Store at room temperature.

• **USP Reference Standards ⟨11⟩**

USP Regorafenib RS

USP Regorafenib Related Compound A RS

4-(4-Amino-3-fluorophenoxy)-*N*-methylpicolinamide.

$C_{13}H_{12}FN_3O_2$ 261.26

USP Sorafenib Tosylate RS

1-[4-Chloro-3-(trifluoromethyl)phenyl]-3-(4-{[2-(methylcarbamoyl)pyridin-4-yl]oxy}phenyl}urea mono(4-methylbenzenesulfonate).

$C_{21}H_{16}ClF_3N_4O_3 \cdot C_7H_8O_3S$ 637.03▲ (USP 1-May-2021)

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

Topic/Question	Contact	Expert Committee
REGORAFENIB	Documentary Standards Support	SM32020 Small Molecules 3
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM32020 Small Molecules 3

Chromatographic Database Information: Chromatographic Database

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