Rivaroxaban Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	26-Jan-2024
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 2

In accordance with the Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Small Molecules 2 Expert Committee intends to revise the Rivaroxaban Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Rivaroxaban Tablets monograph to add *Dissolution Test 3*. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 3*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Yanyin Yang, Senior Scientist II (301-692-3623 or yanyin.yang@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Notice of Intent to Revise
Official: To Be Determined

Rivaroxaban Tablets

DEFINITION

Rivaroxaban Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$).

IDENTIFICATION

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

● **B.** The UV absorption spectrum of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

● **Procedure**

Protect solutions containing rivaroxaban from light.

Solution A: 0.01 M phosphoric acid

Solution B: Acetonitrile

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	92	8
13.0	49	51
13.1	92	8
16.0	92	8

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

Standard solution: 0.2 mg/mL of USP Rivaroxaban RS in *Diluent*

Sample solution: Nominally 0.2 mg/mL of rivaroxaban prepared as follows. Transfer Tablets (NLT 4) into an appropriate volumetric flask. Add a suitable amount of *Diluent* and sonicate to disintegrate and dissolve. Dilute with *Diluent* to volume. Pass the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm. For *Identification B*, use a diode array detector in the range of 200–400 nm.

Column: 4.0-mm × 5.5-cm; 3-µm packing L1

Column temperature: 45°

Flow rate: 1 mL/min

Injection volume: 5 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) in the portion of Tablets 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 = nominal concentration of rivaroxaban in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** ⟨711⟩

▲Test 1▲ (TBD)

Buffer: 0.022 M sodium acetate; adjusted with sodium hydroxide or glacial acetic acid to a pH of 4.5

Medium

For 2.5-mg Tablets: *Buffer*; 900 mL

For 10-mg Tablets: 0.2% sodium dodecyl sulfate in *Buffer*; 900 mL

For 15-mg and 20-mg Tablets: 0.4% sodium dodecyl sulfate in *Buffer*; 900 mL

Apparatus 2: 75 rpm

Times: 15 min for 10-mg, 15-mg, and 20-mg Tablets; 20 min for 2.5-mg Tablets

Mobile phase: Acetonitrile and water (40:60)

Standard stock solution: 0.55 mg/mL of USP Rivaroxaban RS in acetonitrile

Standard solution

For 2.5-mg Tablets: 0.003 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in *Medium*

For 10-mg Tablets: 0.01 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in *Medium*

For 15-mg and 20-mg Tablets: 0.02 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 10-µm pore size.

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

Column: 4.0-mm × 6.0-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 µL for 10-mg, 15-mg, and 20-mg Tablets; 20 µL for 2.5-mg Tablets

Run time: NLT 3 times the retention time of rivaroxaban

System suitability

Sample: *Standard solution*

Suitability requirements

Relative standard deviation: NMT 1.5%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) dissolved:

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

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)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) is dissolved.

▲**Test 3:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 3*.

Protect solutions containing rivaroxaban from light.

Solution A: Dissolve 5 g of sodium hydroxide in 50 mL of water.

Buffer: 0.022 M sodium acetate, pH 4.5 prepared as follows. Dissolve 3 g of sodium acetate in 1 L of water. Adjust with *Solution A* or glacial acetic acid if necessary to a pH of 4.5.

Medium

For 2.5-mg and 10-mg Tablets: Dissolve 2 g of sodium dodecyl sulfate in 1000 mL of *Buffer*; 900 mL

For 15-mg and 20-mg Tablets: Dissolve 4 g of sodium dodecyl sulfate in 1000 mL of *Buffer*; 900 mL

Apparatus 2: 75 rpm

Time: 15 min

Mobile phase: Acetonitrile and water (40:60)

Diluent: Acetonitrile and water (50:50)

Standard stock solution: 0.55 mg/mL of USP Rivaroxaban RS in *Diluent*. Sonicate to dissolve, if necessary.

Standard solution

For 2.5-mg Tablets: 0.003 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in the corresponding *Medium*

For 10-mg Tablets: 0.011 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in the corresponding *Medium*

For 15-mg and 20-mg Tablets: 0.02 mg/mL of USP Rivaroxaban RS from the *Standard stock solution* in the corresponding *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discarding an appropriate volume of filtrate so that a consistent result can be obtained.

[NOTE—The *Sample solution* for 15-mg and 20-mg Tablets may be stable for 20 h at room temperature.]

Chromatographic system

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

Mode: LC

Detector: UV 250 nm

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

Column temperature: 40°

Flow rate: 1.1 mL/min

Injection volume: 10 µL for 10-mg, 15-mg, and 20-mg Tablets; 20 µL for 2.5-mg Tablets

Run time: NLT 3 times the retention time of rivaroxaban

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 2.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) dissolved:

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

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)

V = volume of *Medium*, 900 mL

L = label claim (mg/Tablet)

Tolerances: NLT 80% (*Q*) of the labeled amount of rivaroxaban ($C_{19}H_{18}ClN_3O_5S$) is dissolved. ▲ (TBD)

- **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

- **ORGANIC IMPURITIES**

Protect solutions containing rivaroxaban from light.

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

System suitability solution: 2 µg/mL each of USP Rivaroxaban RS and USP Rivaroxaban Related Compound H RS in *Diluent*

Sensitivity solution: 0.2 µg/mL of USP Rivaroxaban RS from the *Standard solution* in *Diluent*

System suitability

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

[NOTE—See *Table 2* for the relative retention times.]

Suitability requirements

Resolution: NLT 2.0 between rivaroxaban and rivaroxaban related compound H, *System suitability solution*

Relative standard deviation: NMT 1.5%, *Standard solution*

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

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of any unspecified 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 unspecified degradation product 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 = nominal concentration of rivaroxaban in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 2*. The reporting threshold is 0.1%.

Table 2

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Rivaroxaban	1.0	—
Rivaroxaban related compound H[a]	1.2	—
Any unspecified degradation product	—	0.2
Total degradation products	—	0.5

[a] This impurity is included for establishing the *Resolution* requirement in *System suitability*.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.

Add the following:

▲● **Labeling:** The labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

- **USP Reference Standards** ⟨11⟩

USP Rivaroxaban RS

USP Rivaroxaban Related Compound H RS

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

$C_{19}H_{17}Cl_2N_3O_5S$ 470.32

Page Information:

Not Applicable

Current DocID: