Rifabutin Capsules

Type of Posting	Notice of Intent to Revise
Posting Date	17-Nov-2023
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Small Molecules 1

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 1 Expert Committee intends to revise the Rifabutin Capsules monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to revise the Rifabutin Capsules monograph to add *Dissolution Test 2*. *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

Existing references to reagents and reagent names have been updated for consistency with official reagent entry names.

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

Rifabutin Capsules

DEFINITION

Rifabutin Capsules contain NLT 90.0% and NMT 110.0% of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$).

IDENTIFICATION

- **A. Spectroscopic Identification Tests ⟨197⟩, *Ultraviolet-Visible Spectroscopy*:** 197U

  Standard solution: 20 µg/mL of USP Rifabutin RS in methanol, prepared with the aid of sonication. Pass through a filter of 0.5-µm or finer pore size.

  Sample solution: Nominally 20 µg/mL of rifabutin prepared as follows. Suspend a quantity of Capsule contents, equivalent to 200 mg of rifabutin, in 20 mL of methanol. Sonicate for 5 min, and pass through a suitable filter of 0.5-µm or finer pore size. Dilute a portion of the filtrate with methanol to obtain a solution containing 20 µg/mL of rifabutin.

  Acceptance criteria: Meet the requirements

- **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: 13.6 g/L of monobasic potassium phosphate

  Mobile phase: Acetonitrile and *Solution A* (50:50). Adjust with 2 N sodium hydroxide TS to a pH of 6.5 ± 0.1. Pass through a suitable filter of 0.5-µm or finer pore size.

  System suitability solution: Dissolve 10 mg of Rifabutin in 2 mL of methanol, add 1 mL of 2 N sodium hydroxide TS, and allow to stand for 4 min. Add 1 mL of 2 N hydrochloric acid TS, and dilute with *Mobile phase* to 50 mL. [Note—Portions of this solution may be stored in the frozen state for future use.]

  Standard solution: 0.5 mg/mL of USP Rifabutin RS prepared as follows. Transfer an amount of USP Rifabutin RS to a suitable volumetric flask. Add acetonitrile to fill 10% of the volume of the flask, and dilute with *Mobile phase* to volume.

  Sample solution: Nominally 0.5 mg/mL of rifabutin prepared as follows. Remove the contents of NLT 20 Capsules, weigh, and determine the average weight of the Capsule contents. Transfer a portion of the powder, equivalent to 25 mg of rifabutin, to a 50-mL volumetric flask, add 5 mL of acetonitrile, and dilute with *Mobile phase* to volume. Pass through a suitable filter of 0.5-µm or finer pore size.

  Chromatographic system

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

  Mode: LC

  Detector: UV 254 nm

  Column: 4.6-mm × 12.5-cm; 5-µm packing L7

  Flow rate: 1 mL/min

  Injection volume: 10 µL

  Run time: NLT 2 times the retention time of the rifabutin peak

System suitability

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

[NOTE—The chromatogram of the *System suitability solution* exhibits a major peak for a degradant, two minor peaks for degradants, and a major peak for rifabutin at relative retention times of about 0.5, 0.6, 0.8, and 1.0, respectively.]

Suitability requirements

Resolution: NLT 1.3 between the rifabutin peak and the degradant peak eluting at a relative retention time of about 0.8, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) in the portion of Capsules taken:

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

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

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

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

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

Acceptance criteria: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION**

▲Test 1▲ (TBD)

Medium: 0.01 N hydrochloric acid; 900 mL

Apparatus 1: 100 rpm

Time: 45 min

Standard solution: A known concentration of USP Rifabutin RS in *Medium*

Sample solution: A filtered portion of the solution under test, suitably diluted with *Medium* to a concentration similar to that of the *Standard solution*, taking into account its designated potency.

Instrumental conditions

Mode: UV

Analytical wavelength: 280 nm

Analysis

Samples: *Standard solution* and *Sample solution*

Determine the percentage of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) dissolved:

$$(A_U/A_S) \times C_S \times D \times (V/L) \times 100$$

A_U = absorbance of the *Sample solution*

A_S = absorbance of the *Standard solution*

C_S = concentration of the *Standard solution* (mg/mL)

D = dilution factor of the *Sample solution*, if needed

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 75% (Q) of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.01 N hydrochloric acid; 900 mL, deaerated

Apparatus 1: 10–mesh basket; 100 rpm

Time: 60 min

Buffer: Dissolve 13.6 g of potassium phosphate, monobasic in 1 L of water. Adjust with 5 N sodium hydroxide to a pH of 5.7.

Mobile phase: Acetonitrile and *Buffer* (50:50). Adjust with 5 N sodium hydroxide to a pH of 6.5 if necessary.

Standard stock solution: 1.04 mg/mL of USP Rifabutin RS in acetonitrile. Sonicate to dissolve if necessary.

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

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.

Chromatographic system

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

Mode: LC

Detector: UV 280 nm

Column: 4.6-mm × 15-cm; 5-µm packing L7

Column temperature: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

Run time: NLT 1.3 times the retention time of rifabutin

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 rifabutin ($C_{46}H_{62}N_4O_{11}$) dissolved:

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

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

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

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

V = volume of *Medium*, 900 mL

L = label claim (mg/Capsule)

Tolerances: NLT 80% (Q) of the labeled amount of rifabutin ($C_{46}H_{62}N_4O_{11}$) is dissolved.▲ (TBD)

IMPURITIES

- **Organic Impurities**

Solution A: 13.6 g/L of monobasic potassium phosphate in water

Solution B: Acetonitrile and *Solution A* (40:60). Adjust with 2 N sodium hydroxide to a pH of 6.5.

Solution C: Acetonitrile and *Solution A* (70:30). Adjust with 2 N sodium hydroxide to a pH of 6.5.

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution B (%)	Solution C (%)
0	90	10
50	84	16
70	65	35
80	55	45
90	40	60
95	90	10
100	90	10

Diluent: Acetonitrile and *Solution A* (50:50). Adjust with 2 N sodium hydroxide to a pH of 6.5.

System suitability solution: Prepare as directed in the *Assay*.

Standard stock solution: 0.75 mg/mL of USP Rifabutin RS prepared as follows. Transfer an amount of USP Rifabutin RS to a suitable volumetric flask and dissolve it by adding acetonitrile to fill 20% of the final volume of the flask. Sonicate, if necessary. Dilute with *Diluent* to volume.

Standard solution: 0.0075 mg/mL of USP Rifabutin RS in *Diluent* from *Standard stock solution*

Sensitivity solution: 0.75 µg/mL of USP Rifabutin RS in *Diluent* from *Standard solution*

Sample solution: Nominally 0.75 mg/mL of rifabutin prepared as follows. Remove the contents of NLT 20 Capsules as completely as possible, weigh, and determine the average weight of the Capsule contents. Transfer a portion of the crushed powder, equivalent to 75 mg of rifabutin, to a 100-mL volumetric flask and add 20 mL of acetonitrile. Sonicate for 5 min. Add 50 mL of *Diluent* and sonicate for 5 more min. Dilute with *Diluent* to volume. [Note—The *Sample solution* is stable up to 25 h at 10°.]

Chromatographic system

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

Mode: LC

Detector: UV 254 nm

Column: 4.6-mm × 15-cm; 3.5-µm packing L1

Temperatures

Autosampler: 10°

Column: 40°

Flow rate: 1 mL/min

Injection volume: 20 µL

System suitability

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

Suitability requirements

Resolution: NLT 4.0 between the rifabutin 21*R* epimer and rifabutin 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 any individual impurity in the portion of Capsules taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times P \times (F_1/F_2) \times 100$$

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

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

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

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

P = potency of USP Rifabutin RS (µg/mg)

F_1 = conversion factor (0.001 mg/µg)

F_2 = relative response factor (see *Table 2*)

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

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Rifabutin *N*-oxide[a]	0.3	0.72	0.70
16-Desacetylrifabutin[b]	0.40	0.92	1.0
Rifabutin 14*R* epimer[c]	0.63	0.89	1.0
3-Aminorifamycin S[d,e]	0.73	—	—
Rifabutin 21*R* epimer[f]	0.82	0.86	1.0
Rifabutin	1.0	1.0	—
Didehydrorifabutin[g]	1.60	1.0	0.50
Any unspecified impurity	—	1.0	0.20
Total impurities	—	—	4.5

[a] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-16-Acetyloxy-6,18,20-trihydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26(3*H*,9*H*)-trione 1′-oxide.

[b] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,16,18,20-Tetrahydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethylspiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-5,10,26(3*H*,9*H*)-trione.

[c] (9*S*,12*E*,14*R*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,18,20-Trihydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-16-yl acetate.

[d] (2*S*,12*Z*,14*E*,16*S*,17*S*,18*R*,19*R*,20*R*,21*S*,22*R*,23*S*,24*E*)-8-Amino-5,17,19-trihydroxy-23-methoxy-2,4,12,16,18,20,22-heptamethyl-1,6,9,11-tetraoxo-1,2,6,9-tetrahydro-2,7-(epoxypentadeca[1,11,13]trienimino)naphtho[2,1-b]furan-21-yl acetate.

[e] This is a process impurity and is not included in total impurities.

[f] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*R*,22*E*,24*Z*)-6,18,20-Trihydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-16-yl acetate.

[g] (9*S*,12*E*,14*S*,15*R*,16*S*,17*R*,18*R*,19*R*,20*S*,21*S*,22*E*,24*Z*)-6,18,20-Trihydroxy-1′-isobutyl-14-methoxy-7,9,15,17,19,21,25-heptamethyl21-methylene-5,10,26-trioxo-3,5,9,10-tetrahydrospiro[9,4-(epoxypentadeca[1,11,13]trienimino)-2*H*-furo[2′,3′:7,8]naphtho[1,2-*d*]imidazole-2,4′-piperidine]-16-yl acetate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers, protected from light and from excessive heat. 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 Rifabutin RS

Page Information:

Not Applicable

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