Rufinamide Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	28–Feb–2020
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Expert Committee	Chemical Medicines Monographs 4

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 4 Expert Committee intends to revise the Rufinamide Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to accommodate drug products with different dissolution conditions and tolerances than the existing dissolution test.

- *Dissolution Test 2* was validated using an Inertsil ODS-3V brand of column with L1 packing. The typical retention time for rufinamide is about 3.1 min.

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 Claire Chisolm, Scientific Liaison to the Chemical Medicines Monographs 4 Expert Committee (301-230-3215 or cnc@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*.

Rufinamide Tablets

DEFINITION

Rufinamide Tablets contain an amount of Rufinamide equivalent to NLT 95.0% and NMT 105.0% of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$).

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*.

ASSAY

- **PROCEDURE**

Buffer: 2.7 g/L of potassium dihydrogen phosphate in water
Diluent: Acetonitrile, methanol, and water (40:50:10)
Mobile phase: Methanol, tetrahydrofuran, and *Buffer* (15:5:80)
System suitability stock solution: 0.8 mg/mL of USP Rufinamide RS, and 0.02 mg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS in *Diluent*. [NOTE—USP Rufinamide Related Compound B RS is used for identification purposes only.]
System suitability solution: 0.08 mg/mL of USP Rufinamide RS, and 2 µg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS, in *Buffer* from the *System suitability stock solution*
Standard stock solution: 0.8 mg/mL of USP Rufinamide RS in *Diluent*
Standard solution: 0.08 mg/mL of USP Rufinamide RS in *Buffer* from the *Standard stock solution*
Sample stock solution: Nominally 0.8 mg/mL of rufinamide in *Diluent* from a portion of NLT 20 finely powdered Tablets. Sonicate for 10 min, and shake for 15 min. Centrifuge a portion of the suspension.
Sample solution: 0.08 mg/mL of rufinamide in *Buffer*, from a portion of suspension obtained from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 210 nm
Column: 4.6-mm × 12.5-cm; 5-µm packing L1
Flow rate: 1 mL/min
Injection volume: 25 µL
Run time: 2.3 times the retention time of the rufinamide peak
System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—For relative retention times refer to *Table 9* in *Organic Impurities*.]
Suitability requirements
Resolution: NLT 1.5 between rufinamide and rufinamide related compound A, *System suitability solution*
Tailing factor: NMT 1.5, *Standard solution*
Relative standard deviation: NMT 2.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of rufinamide ($C_{10}H_8F_2N_4O$) in the portion of Tablets taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of USP Rufinamide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of rufinamide in the *Sample solution* (mg/mL)

Acceptance criteria: 95.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (TBD)
Medium 1: 0.1 N hydrochloric acid
Medium 2: pH 6.8 phosphate buffer
Apparatus 4: With 22.6-mm cell, glass beads in the cone, with Tablet laying on the beads. Insert 320–350 mg of glass wool in the filter insert and then a glass microfiber filter of 2.7-µm pore size and a glass microfiber filter of 0.7-µm pore size.
Times: 5 and 12 h for the 200-mg Tablets; 6 and 16 h for the 400-mg Tablets
Flow rate: 16 mL/min, pulsating
Test intervals, media, and sample solutions for the 200-mg Tablets: See *Table 1*.

Table 1

Samples	Interval (min)	Volume (mL)	Medium
1	60	50	1
2	120	50	2
1	60	50	2
3	120	50	2

Test intervals (I_i): See *Table 2*.

Table 2

Interval	Time (min)
I_1	0–60
I_2	60–180
I_3	180–300
I_4	300–360
I_5	360–480
I_6	480–600
I_7	600–720

Sample solutions (V_i): See *Table 3*.

Table 3

V_1	eluate of test interval I_1; volume = 960 mL
V_2 to V_3	eluate of test interval I_2 to I_3; volume = 1920 mL, each
V_4	eluate of test interval I_4; volume 960 mL
V_5 to V_7	eluate of test interval I_5 to I_7; volume = 1920 mL, each

Test intervals, media, and sample solutions for the 400-mg Tablets: See *Table 4*.

Table 4

Samples	Interval (min)	Volume (mL)	Medium
1	60	50	1

Table 4 *(continued)*

Samples	Interval (min)	Volume (mL)	Medium
1	60	50	2
3	120	50	2
1	120	50	2
2	180	50	2

Test intervals (I_i): See *Table 5*.

Table 5

Interval	Time (min)
I_1	0–60
I_2	60–120
I_3	120–240
I_4	240–360
I_5	360–480
I_6	480–600
I_7	600–780
I_8	780–960

Sample solutions (V_i): See *Table 6*.

Table 6

V_1	eluate of test interval I_1; volume = 960 mL
V_2	eluate of test interval I_2; volume = 960 mL
V_3 to V_6	eluate of test interval I_3 to I_6; volume = 1920 mL, each
V_7 to V_8	eluate of test interval I_7 to I_8; volume = 2880 mL, each

Mobile phase: Water, methanol, tetrahydrofuran, and acetic acid (100: 50: 13: 0.12), with the addition of 206 mg of sodium pentanesulfonate, monohydrate
Standard stock solution: 600 µg/mL of USP Rufinamide RS in methanol
Standard solution 1: 60 µg/mL of rufinamide in *Medium 1* from the *Standard stock solution*
Standard solution 2: 60 µg/mL of rufinamide in *Medium 2* from the *Standard stock solution*
Standard solution 3: 12 µg/mL of rufinamide prepared as follows. Transfer 10 mL of the *Standard stock solution* to a 500-mL volumetric flask, add 40 mL of methanol, and dilute with *Medium 2* to volume.
Standard solution 4: 6 µg/mL of rufinamide in *Medium 2* from *Standard solution 3*
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 25-cm; 10-µm packing L1
Flow rate: 1.2 mL/min
Injection volume: 20 µL
Run time: 1.4 times the retention time of the rufinamide peak
System suitability
Sample: *Standard solution 1*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Calculate the percentage of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) [$f(S_i)$] dissolved in the *Sample solution* (S_i) by the following steps:
Calculate the regression line for the *Standard solutions*:

$$y = ax + b$$

y = peak area of rufinamide from the *Standard solution*
x = concentration of rufinamide in the *Standard solution* (µg/mL)

$$f(S_i) = [(y - b)/a] \times [(V_i)/(1000 \times L)] \times 100$$

y = peak area of rufinamide from the *Sample solution*
b = y-intercept
a = slope
L = label claim (mg/Tablet)
V_i = volume of *Sample solution* (mL)

Cumulative percentage of the Tablet label claim dissolved:

$$F\left(I_j\right) = \sum_{i=1}^{i} f\left(S_i\right)$$

i,j = indices of test interval

Tolerances
For Tablets labeled to contain 200 mg: See *Table 7*.

Table 7

Time (h)	Amount Released
5	NLT 60%
12	NLT 80%

For Tablets labeled to contain 400 mg: See *Table 8*.

Table 8

Time (h)	Amount Released
6	NLT 60%
16	NLT 80%

The percentages of the labeled amount of rufinamide dissolved in the times specified conform to *Dissolution* ⟨711⟩, *Acceptance Table 2*.
▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.
Medium: pH 6.8 sodium phosphate buffer containing 2% sodium dodecyl sulfate (7.8 g/L of monobasic sodium phosphate dihydrate and 0.89 g/L of sodium hydroxide in water, adjusted with phosphoric acid or 1 N sodium hydroxide VS to a pH of 6.8; to each liter of this solution add 20.0 g of sodium dodecyl sulfate and sonicate to dissolve); 2000 mL
Apparatus 2: 50 rpm
Time: 1 h for 100-mg and 200-mg Tablets; 4 h for 400-mg Tablets
Buffer: 6.8 g/L of monobasic potassium phosphate in water
Mobile phase: Acetonitrile and *Buffer* (30:70)
Standard stock solution: 1 mg/mL of USP Rufinamide RS in methanol
Standard solution: 0.05 mg/mL of USP Rufinamide RS from the *Standard stock solution* diluted with *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size, discard the first few milliliters, and dilute with *Medium* if necessary.

Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 220 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume: 5 µL
Run time: NLT 2 times the retention time of the rufinamide peak

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) dissolved:

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

r_U = peak response of rufinamide from the *Sample solution*
r_S = peak response of rufinamide from the *Standard solution*
C_S = concentration of USP Rufinamide RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 2000 mL
D = dilution factor of the *Standard solution*
L = label claim of rufinamide (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of rufinamide ($C_{10}H_8F_2N_4O$) is dissolved.▲ (TBD)

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

IMPURITIES

• **Organic Impurities**

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

System suitability stock solution: 0.8 mg/mL of USP Rufinamide RS, and 0.02 mg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS in *Diluent*. [Note—USP Rufinamide Related Compound B RS is used for identification purposes.]

System suitability solution: 0.08 mg/mL of USP Rufinamide RS, and 2 µg/mL each of USP Rufinamide Related Compound A RS and USP Rufinamide Related Compound B RS, in *Buffer* from the *System suitability stock solution*

Standard stock solution: 0.8 mg/mL of USP Rufinamide RS in *Diluent*

Standard solution: 0.4 µg/mL of USP Rufinamide RS from the *Standard stock solution* prepared as follows. Pipet a suitable volume of *Standard stock solution* to a volumetric flask. Add *Diluent* to fill 10% of final volume, and dilute with *Buffer* to volume.

System suitability
Samples: *System suitability solution* and *Standard solution*
[Note—For relative retention times refer to *Table 9*.]
Suitability requirements
Resolution: NLT 1.5 between rufinamide and rufinamide related compound A, *System suitability solution*
Tailing factor: NMT 1.5 for rufinamide, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*

Analysis
Samples: *Sample solution* and *Standard solution*
Calculate the percentage of any individual 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 individual impurity from the *Sample solution*
r_S = peak response of rufinamide from the *Standard solution*
C_S = concentration of USP Rufinamide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of rufinamide in the *Sample solution* (mg/mL)

Acceptance criteria: See *Table 9*.

Table 9

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Rufinamide	1.0	—
Rufinamide related compound A[a]	1.2	—
Rufinamide related compound B[b]	1.8	—
Any individual unspecified degradation product	—	0.1
Total impurities	—	0.5

[a] 1-(2-Fluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.
[b] Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate.

ADDITIONAL REQUIREMENTS

• **Packaging and Storage:** Preserve in tight containers. Store at controlled room temperature.

Add the following:

▲• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (TBD)

• **USP Reference Standards** ⟨11⟩
USP Rufinamide RS
USP Rufinamide Related Compound A RS
1-(2-Fluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.
$C_{10}H_9FN_4O$ 220.20
USP Rufinamide Related Compound B RS
Methyl 1-(2,6-difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxylate.
$C_{11}H_9F_2N_3O_2$ 253.20