Rufinamide Tablets

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Notice of Intent to Revise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posting Date</td>
<td>28–Feb–2020</td>
</tr>
<tr>
<td>Targeted Official Date</td>
<td>To Be Determined, Revision Bulletin</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 4</td>
</tr>
</tbody>
</table>

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_{12}F_{2}N_{4}O).

**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.]

**Standard stock solution:** 0.8 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 solution:** 0.08 mg/mL of USP Rufinamide RS in Diluent

**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_{12}F_{2}N_{4}O) in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_u}{r_s} \right) \times \left( \frac{C_s}{C_I} \right) \times 100 \]

- \( r_u \) = 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**
- **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>
<thead>
<tr>
<th>Samples</th>
<th>Interval (min)</th>
<th>Volume (mL)</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>50</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>120</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>60</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>50</td>
<td>2</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Interval</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I_1</td>
<td>0–60</td>
</tr>
<tr>
<td>I_2</td>
<td>60–180</td>
</tr>
<tr>
<td>I_3</td>
<td>180–300</td>
</tr>
<tr>
<td>I_4</td>
<td>300–360</td>
</tr>
<tr>
<td>I_5</td>
<td>360–480</td>
</tr>
<tr>
<td>I_6</td>
<td>480–600</td>
</tr>
<tr>
<td>I_7</td>
<td>600–720</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>V_1</th>
<th>eluate of test interval I_1; volume = 960 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>V_1 to V_7</td>
<td>eluate of test interval I_1 to I_7; volume = 1920 mL, each</td>
</tr>
<tr>
<td>V_7</td>
<td>eluate of test interval I_7; volume = 960 mL</td>
</tr>
<tr>
<td>V_7 to V_1</td>
<td>eluate of test interval I_7 to I_1; volume = 1920 mL, each</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Samples</th>
<th>Interval (min)</th>
<th>Volume (mL)</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>50</td>
<td>1</td>
</tr>
</tbody>
</table>
2 Rufinamide

**Table 4 (continued)**

<table>
<thead>
<tr>
<th>Samples</th>
<th>Interval (min)</th>
<th>Volume (mL)</th>
<th>Medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>60</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>3</td>
<td>120</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>1</td>
<td>120</td>
<td>50</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>180</td>
<td>50</td>
<td>2</td>
</tr>
</tbody>
</table>

Test intervals (Ii): See Table 5.

**Table 5**

<table>
<thead>
<tr>
<th>Interval</th>
<th>Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>i1</td>
<td>0–60</td>
</tr>
<tr>
<td>i2</td>
<td>60–120</td>
</tr>
<tr>
<td>i3</td>
<td>120–240</td>
</tr>
<tr>
<td>i4</td>
<td>240–360</td>
</tr>
<tr>
<td>i5</td>
<td>360–480</td>
</tr>
<tr>
<td>i6</td>
<td>480–600</td>
</tr>
<tr>
<td>i7</td>
<td>600–780</td>
</tr>
<tr>
<td>i8</td>
<td>780–960</td>
</tr>
</tbody>
</table>

Sample solutions (Vi): See Table 6.

**Table 6**

<table>
<thead>
<tr>
<th>Vi</th>
<th>eluate of test interval i1; volume = 960 mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>V1 to V4</td>
<td>eluate of test interval i1 to i4; volume = 1920 mL, each</td>
</tr>
<tr>
<td>V5 to V8</td>
<td>eluate of test interval i1 to i8; volume = 2880 mL, each</td>
</tr>
</tbody>
</table>

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 (C10H16F2N2O) [f(Si)] dissolved in the Sample solution (Si) by the following steps:

Calculate the regression line for the Standard solutions:

\[ y = ax + b \]

\[ y = \text{peak area of rufinamide from the Standard solution} \]

\[ x = \text{concentration of rufinamide in the Standard solution (µg/mL)} \]

\[ f(S) = \frac{[(y - b)/a] \times [(V)/(1000 \times L)]}{100} \]

\[ y = \text{peak area of rufinamide from the Sample solution} \]

\[ b = y\text{-intercept} \]

\[ a = \text{slope} \]

\[ L = \text{label claim (mg/Tablet)} \]

\[ V_i = \text{volume of Sample solution (mL)} \]

Cumulative percentage of the Tablet label claim dissolved:

\[ F(i) = \sum_{i=1}^{i} f(S_i) \]

\[ i_j = \text{indices of test interval} \]

**Tolerances**

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

**Table 7**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>NLT 60%</td>
</tr>
<tr>
<td>12</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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

**Table 8**

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>Amount Released</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>NLT 60%</td>
</tr>
<tr>
<td>16</td>
<td>NLT 80%</td>
</tr>
</tbody>
</table>

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

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C238423-M4108-CHM42015, rev. 00 20200228
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 (C₁₉H₁₅F₂N₂O) dissolved:

\[
\text{Result} = \left( \frac{r_f}{r_s} \times C_s \times V \times D \times (1/L) \times 100 \right)
\]

\[r_f\] = 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 (C₁₉H₁₅F₂N₂O) 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:

\[
\text{Result} = \left( \frac{r_f}{r_s} \times \frac{C_s}{C_U} \times 100 \right)
\]

\[r_f\] = 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>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rufinamide</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Rufinamide related compound A</td>
<td>1.2</td>
<td>—</td>
</tr>
<tr>
<td>Rufinamide related compound B</td>
<td>1.8</td>
<td>—</td>
</tr>
<tr>
<td>Any individual unspecified degradation product</td>
<td>—</td>
<td>0.1</td>
</tr>
<tr>
<td>Total impurities</td>
<td>—</td>
<td>0.5</td>
</tr>
</tbody>
</table>

\(a\) 1-(2-Fluorobenzyl)-1H-1,2,3-triazole-4-carboxamide.

\(b\) Methyl 1-(2,6-difluorobenzyl)-1H-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)-1H-1,2,3-triazole-4-carboxamide.
  \(C_{11}H_{15}F_2N_2O_6\) 220.20
  USP Rufinamide Related Compound B RS
  Methyl 1-(2,6-difluorobenzyl)-1H-1,2,3-triazole-4-carboxylate.
  \(C_{11}H_{15}F_2N_2O_6\) 253.20