### Rosuvastatin Tablets

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Revision Bulletin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posting Date</td>
<td>27–July–2018</td>
</tr>
<tr>
<td>Official Date</td>
<td>01–August–2018</td>
</tr>
<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 2</td>
</tr>
<tr>
<td>Reason for Revision</td>
<td>Compliance</td>
</tr>
</tbody>
</table>

In accordance with the Rules and Procedures of the 2015–2020 Council of Experts, the Chemical Medicines Monographs 2 Expert Committee has revised the Rosuvastatin Tablets monograph. The purpose for the revision is to add *Dissolution Test 3* to accommodate drug products that were approved with different conditions and tolerances.

The Rosuvastatin Tablets Revision Bulletin supersedes the Rosuvastatin Tablets monograph that is becoming official in the *First Supplement to USP 41–NF 36*.

Should you have any questions, please contact Donald Min, Ph.D., Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@usp.org).
Rosuvastatin Tablets

**DEFINITION**
Rosuvastatin Tablets contain NLT 90% and NMT 110% of the labeled amount of rosuvastatin (C27H38FN1O8S).

**IDENTIFICATION**
- **A.** The UV absorption spectra of the rosuvastatin peak of the Sample solution exhibit maxima and minima at the same wavelengths as those of the corresponding peak of the Standard solution, as obtained in the Assay.
- **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**
  - Protect all solutions containing rosuvastatin from light.
  - **Solution A:** 1% trifluoroacetic acid in water
  - **Mobile phase:** Acetonitrile, Solution A, and water (37:1:62)
  - **Diluent:** Acetonitrile and water (25:75)
  - **Standard stock solution:** 1 mg/mL of USP Rosuvastatin Calcium RS prepared as follows. To a suitable amount of USP Rosuvastatin Calcium RS in a suitable volumetric flask, add water equal to about 50% of the flask volume. Vigorously mix or sonicate the flask to dissolve the material. Add acetonitrile equal to about 25% of the total volume and then dilute with water to volume.
  - **Standard solution:** 25 µg/mL of USP Rosuvastatin Calcium RS in Diluent from the Standard stock solution
  - **Sample solution:** Nominally 25 µg/mL of rosuvastatin prepared as follows. Transfer a suitable number of Tablets, NLT 5 Tablets for 80-mg Tablet strength and NLT 10 Tablets for all other Tablet strengths, into a suitable extraction flask. Add water and vigorously mix to disintegrate the Tablets. Add acetonitrile and mix vigorously. Add more water to obtain a 25:75 composition of acetonitrile and water. Pass the solution through a suitable filter. Dilute the filtrate with Diluent, if necessary, to the desired concentration.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 242 nm
- **Column:** 3.2-mm × 25-cm; 5-µm packing L1. [Note—A suitable guard column may be used.]
- **Column temperature:** 40°C
- **Flow rate:** 0.75 mL/min
- **Injection volume:** 10 µL
- **Run time:** NLT 1.3 times the retention time of rosuvastatin

**System suitability**
- **Sample:** Standard solution
- **Suitability requirements**
  - Tailing factor: NMT 1.8
  - Relative standard deviation: NMT 2.0%
- **Analysis**
  - **Samples:** Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of rosuvastatin (C27H38FN1O8S) dissolved:

\[
\text{Result} = \left( \frac{r_s}{r_u} \right) \times \frac{C_s}{C_u} \times \left( \frac{1}{L} \right) \times M \times \left( \frac{M_1}{M_2} \right) \times 100
\]

where
- \( r_s \) = peak response of rosuvastatin from the Sample solution
- \( C_s \) = concentration of USP Rosuvastatin RS in the Standard solution (µg/mL)
- \( C_u \) = nominal concentration of rosuvastatin in the Sample solution (µg/mL)
- \( M \) = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
- \( M_1 \) = molecular weight of rosuvastatin, 481.54
- \( M_2 \) = molecular weight of rosuvastatin calcium, 1001.14

**Acceptance criteria:** NMT 1.5

**PERFORMANCE TESTS**

**Dissolution**
- **Medium:** Citrate buffer, pH 6.6 (prepare a solution of 14.7 g/L of sodium citrate dihydrate and 0.33 g/L of anhydrous citric acid; adjust if necessary with sodium citrate or citric acid to a pH of 6.6); 900 mL
- **Apparatus 2:** 50 rpm
- **Time:** 30 min
- **Diluent:** Acetonitrile and water (25:75)
- **Mobile phase:** Acetonitrile, water, and phosphoric acid (400:600:1)

**Sample solution:** A solution of concentration similar to the Sample solution in Medium from the Standard stock solution

**Sample solution:** Pass a portion of the solution under test through a suitable filter.

**Chromatographic system**
(See Chromatography (621), System Suitability.)
- **Mode:** LC
- **Detector:** UV 242 nm
- **Column:** 4.6-mm × 5-cm; 5-µm packing L1
- **Flow rate:** 1 mL/min
- **Injection volume:** 20 µL
- **Run time:** NLT 2.5 times the retention time of rosuvastatin

**System suitability**
- **Sample:** Standard solution
- **Suitability requirements**
  - Tailing factor: NMT 1.5
- **Analysis**
  - **Samples:** Standard solution and Sample solution
  - Calculate the percentage of the labeled amount of rosuvastatin (C27H38FN1O8S) dissolved:

\[
\text{Result} = \left( \frac{r_s}{r_u} \right) \times C_s \times \left( \frac{1}{L} \right) \times M \times \left( \frac{M_1}{M_2} \right) \times 100
\]
2 Rosuvastatin

Tolerances: NLT 75% (Q) of the labeled amount of rosuvastatin (C₂₂H₂₈FN₃O₈S) is dissolved.

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

Medium: 0.05 M citrate buffer pH 6.6 (to a solution of 10.5 g/L of citric acid monohydrate, add 5.9 g/L of sodium hydroxide and mix; adjust with 0.2 M sodium hydroxide or 0.2 M hydrochloric acid to a pH of 6.6); 900 mL

Apparatus 2: 50 rpm
Time: 30 min
Buffer: Dissolve 2.72 g of potassium dihydrogen phosphate in 1 L of water and add 2 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and Buffer (30:70)

Standard stock solution: 0.5 mg/mL of USP Rosuvastatin Calcium RS in Medium. Sonication may be necessary for complete dissolution.

Standard solution: (L/900) mg/mL of USP Rosuvastatin Calcium RS in Medium from the Standard stock solution

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system
(See Chromatography (621), System Suitability.)

Mode: LC
Detector: UV 240 nm
Column: 4.6-mm × 10-cm; 5-µm packing L1
Flow rate: 2 mL/min
Injection volume: 20 µL
Run time: NLT 1.5 times the retention time of rosuvastatin

System suitability
Sample: Standard solution
Suitability requirements

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of rosuvastatin (C₂₂H₂₈FN₃O₈S) dissolved:

\[ \text{Result} = \left( \frac{A_u}{A_s} \right) \times C_s \times V \times (1/L) \times \left[ M \times \left( \frac{M_1}{M_2} \right) \right] \times 100 \]

- \( A_u \) = absorbance of the Sample solution
- \( A_s \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Rosuvastatin Calcium RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( M \) = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
- \( M_1 \) = molecular weight of rosuvastatin, 481.54
- \( M_2 \) = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (Q) of the labeled amount of rosuvastatin (C₂₂H₂₈FN₃O₈S) is dissolved.

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

Medium: 0.05 M citrate buffer pH 6.6 (dissolve 63.0 g of citric acid monohydrate and 35.2 g of sodium hydroxide in 10.5 L of water and mix; adjust if necessary with sodium hydroxide or citric acid to a pH of 6.6); 900 mL

Apparatus 2: 50 rpm
Time: 45 min

Standard stock solution: 0.044 mg/mL of USP Rosuvastatin Calcium RS in Medium. Sonication may be necessary for complete dissolution.

Standard solution: (L/900) mg/mL of USP Rosuvastatin Calcium RS in Medium from the Standard stock solution, where \( L \) is the label claim in mg/Tablet. [Note—The Standard stock solution is the Standard solution for 40-mg Tablets.]

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Instrumental conditions
Mode: UV
Analytical wavelength: 241 nm
Cell: 1.0 cm (for 5-mg and 10-mg Tablets) and 0.2 cm (for 20-mg and 40-mg Tablets)
Blank: Medium

Analysis
Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of rosuvastatin (C₂₂H₂₈FN₃O₈S) dissolved:

\[ \text{Result} = \left( \frac{A_u}{A_s} \right) \times C_s \times V \times (1/L) \times \left[ M \times \left( \frac{M_1}{M_2} \right) \right] \times 100 \]

- \( A_u \) = absorbance of the Sample solution
- \( A_s \) = absorbance of the Standard solution
- \( C_s \) = concentration of USP Rosuvastatin Calcium RS in the Standard solution (mg/mL)
- \( V \) = volume of Medium, 900 mL
- \( L \) = label claim (mg/Tablet)
- \( M \) = number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
- \( M_1 \) = molecular weight of rosuvastatin, 481.54
- \( M_2 \) = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (Q) of the labeled amount of rosuvastatin (C₂₂H₂₈FN₃O₈S) is dissolved.

Uniformity of Dosage Units (905): Meet the requirements

Impurities

Organic impurities
Protect all solutions containing rosuvastatin calcium from light.

Mobile phase and Diluent: Prepare as directed in the Assay.

System suitability stock solution: 50 µg/mL each of USP Rosuvastatin Calcium RS and rosuvastatin diastereomers in acidic water prepared as follows. To a suitable amount of USP Rosuvastatin Calcium RS in a suitable volumetric flask, add water equal to about 50% of the flask volume. Add 1 M hydrochloric acid equal to about 10% of the total volume. Heat in a water bath at 60° for 2 h and neutralize by adding 1 M sodium hydroxide. Cool to room temperature and add acetonitrile equal to about 25% of the total volume. Dilute with water to volume.

System suitability solution: 25 µg/mL each of USP Rosuvastatin Calcium RS and rosuvastatin diastereomers prepared by mixing System suitability stock solution and Diluent (1:1)

Standard solution: 10 µg/mL of USP Rosuvastatin Calcium RS in Diluent

Sample solution: Nominal 1 mg/mL of rosuvastatin prepared as follows. Transfer a number of Tablets per Table 1 into a suitable extraction flask. Add water, and mix vigorously to disintegrate the Tablets. Add acetonitrile and mix vigorously followed by an additional amount of water to obtain a final composition of...
acetonitrile and water (1:3). Pass the solution through a suitable filter.

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Number of Tablets</th>
<th>Volumetric Flask Size (mL)</th>
<th>Water (mL)</th>
<th>Acetonitrile (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>40</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>200</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>12</td>
<td>500</td>
<td>250</td>
<td>125</td>
</tr>
<tr>
<td>80</td>
<td>6</td>
<td>500</td>
<td>250</td>
<td>125</td>
</tr>
</tbody>
</table>

Chromatographic system: Proceed as directed in the Assay, except for Run time.

<table>
<thead>
<tr>
<th>Tablet Strength (mg)</th>
<th>Number of Tablets</th>
<th>Volumetric Flask Size (mL)</th>
<th>Water (mL)</th>
<th>Acetonitrile (mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5</td>
<td>40</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>20</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>10</td>
<td>10</td>
<td>100</td>
<td>50</td>
<td>25</td>
</tr>
<tr>
<td>20</td>
<td>10</td>
<td>200</td>
<td>100</td>
<td>50</td>
</tr>
<tr>
<td>40</td>
<td>12</td>
<td>500</td>
<td>250</td>
<td>125</td>
</tr>
<tr>
<td>80</td>
<td>6</td>
<td>500</td>
<td>250</td>
<td>125</td>
</tr>
</tbody>
</table>

Run time: NLT 2.5 times the retention time of rosuvastatin

System suitability

Samples: System suitability solution and Standard solution

Suitability requirements

Resolution: NLT 1.5 between rosuvastatin and rosuvastatin diastereomers, System suitability solution

Tailing factor: NMT 1.8, Standard solution

Relative standard deviation: NMT 2.0%, Standard solution

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of each impurity in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left[ \frac{M_{r1}}{M_{r2}} \right] \times (1/F) \times 100
\]

- \( r_U \): peak response of each impurity from the Sample solution
- \( r_S \): peak response of rosuvastatin from the Standard solution
- \( C_S \): concentration of USP Rosuvastatin Calcium RS in the Standard solution (mg/mL)
- \( C_U \): nominal concentration of rosuvastatin in the Sample solution (mg/mL)
- \( M \): number of moles of rosuvastatin per mole of rosuvastatin calcium, 2
- \( M_{r1} \): molecular weight of rosuvastatin, 481.54
- \( M_{r2} \): molecular weight of rosuvastatin calcium, 1001.14
- \( F \): relative response factor (see Table 2)

Acceptance criteria: See Table 2.

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rosuvastatin related compound A</td>
<td>0.9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rosuvastatin diastereomers(^{a,b})</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rosuvastatin ketone(^{c})</td>
<td>1.6</td>
<td>0.71</td>
<td>2.1</td>
</tr>
<tr>
<td>Rosuvastatin lactone(^{d})</td>
<td>2.3</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Rosuvastatin ethyl ester (if present)(^{e})</td>
<td>3.8</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
<td>1.0</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>3.6</td>
</tr>
</tbody>
</table>

\(^{a}\) \((3R,5R,\xi)-7\{4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl\}-3,5-dihydroxyhept-6-enoic acid.

\(^{b}\) Process impurity controlled in the drug substance monograph. Provided for information only; the content is not calculated, not reported, and not included in the total impurities.

\(^{c}\) \((R,\xi)-7\{4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl\}-3-hydroxy-5-oxohept-6-enoic acid.

\(^{d}\) \(N\{4-(4-Fluorophenyl)-5-\xi-(E)-2-\{[(2S,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]vinyl\}-6-isopropylpyrimidin-2-yl\}-N-methylmethanesulfonamide.

\(^{e}\) Ethyl \((3R,5S,\xi)-7\{4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl\}-3,5-dihydroxyhept-6-enoate.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in well-closed containers. Store at controlled room temperature.
- **Labeling:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.
- **USP Reference Standards (11)**
  - USP Rosuvastatin Calcium RS\(^{\text{a}}\) 15 (USP41)

© 2018 The United States Pharmacopeial Convention All Rights Reserved.