Rosuvastatin Tablets

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Reason for Revision: Compliance

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 4 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 4* was validated using the Waters XBridge C18 brand of column with L1 packing. The typical retention time for rosuvastatin is about 2.1 min.

The Rosuvastatin Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Yanyin Yang, Associate Scientific Liaison (301-692-3623 or yanyin.yang@usp.org).
Rosuvastatin Tablets

DEFINITION
Rosuvastatin Tablets contain NLT 90% and NMT 110% of the labeled amount of rosuvastatin (C_{27}H_{35}FN_{3}O_{5}S).

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 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. For Identification A, use a diode array detector in the range of 200–440 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: 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
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of rosuvastatin in Tablets taken:

\[
\text{Result} = \left( \frac{r_f}{r_s} \right) \times \left( \frac{C_f}{C_s} \right) \times \left[ \frac{M \times (M_1/M_2)}{V} \right] \times 100
\]

\[
C_f = \text{concentration of USP Rosuvastatin in the Standard solution (µg/mL)}
\]
\[
C_s = \text{nominal concentration of rosuvastatin in the Sample solution (µg/mL)}
\]
\[
M = \text{number of moles of rosuvastatin per mole of rosuvastatin calcium, 2}
\]
\[
M_1 = \text{molecular weight of rosuvastatin calcium, 1001.14}
\]
\[
M_2 = \text{molecular weight of rosuvastatin, 481.54}
\]

Acceptance criteria: 90%–110%

PERFORMANCE TESTS

• DISSOLUTION (711)
Protect all solutions containing rosuvastatin from light.
Test 1
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)
Standard stock solution: 1 mg/mL of USP Rosuvastatin Calcium RS in Diluent
Standard 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 in Tablets:

\[
\text{Result} = \left( \frac{r_f}{r_s} \right) \times C_f \times V \times (1/L) \times \left[ \frac{M \times (M_1/M_2)}{V} \right] \times 100
\]

\[
r_f = \text{peak response of rosuvastatin from the Sample solution}
\]
\[
r_s = \text{peak response of rosuvastatin from the Standard solution}
\]
\[
C_f = \text{concentration of USP Rosuvastatin in the Standard solution (µg/mL)}
\]
\[
V = \text{volume of Medium, 900 mL}
\]
\[
L = \text{label claim (mg/Tablet)}
\]
\[
M = \text{number of moles of rosuvastatin per mole of rosuvastatin calcium, 2}
\]
\[
M_1 = \text{molecular weight of rosuvastatin calcium, 1001.14}
\]
\[
M_2 = \text{molecular weight of rosuvastatin, 481.54}
\]
Tolerances: NLT 75% (Q) of the labeled amount of rosuvastatin \((C_{22}H_{28}FN_{2}O_{9}S)\) 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**

**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 rosuvastatin \((C_{22}H_{28}FN_{2}O_{9}S)\) dissolved:

Result = \(\left( \frac{r_1}{r_2} \right) \times C_1 \times V \times \left( \frac{1}{L} \right) \times \left( M \times \left( \frac{M_{12}}{M_{11}} \right) \right) \times 100\)

\(r_0\) = peak response of rosuvastatin from the Sample solution

\(r_1\) = peak response of rosuvastatin from the Standard solution

\(C_1\) = 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

\(M_{11}\) = molecular weight of rosuvastatin, 481.54

\(M_{12}\) = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (Q) of the labeled amount of rosuvastatin \((C_{22}H_{28}FN_{2}O_{9}S)\) is dissolved.

**Test 4:** If the product complies with this test, the labeling indicates that it meets Dissolution Test 4.

**Medium:** 0.05 M sodium 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 10% w/v sodium citrate dihydrate solution or 10% w/v anhydrous citric acid solution to a pH of 6.6); 900 mL

**Apparatus 1:** 100 rpm

**Time:** 30 min

**Solution A:** Acetonitrile and water (25:75)

**Mobile phase:** Acetonitrile, phosphoric acid, and water (40:0.1:60)

**Standard stock solution:** 1.04 mg/mL of USP Rosuvastatin Calcium RS in Solution A. 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 \((C_{22}H_{28}FN_{2}O_{9}S)\) dissolved:

Result = \(\left( \frac{A_0}{A_1} \right) \times C_1 \times V \times \left( \frac{1}{L} \right) \times \left( M \times \left( \frac{M_{12}}{M_{11}} \right) \right) \times 100\)

\(A_0\) = absorbance of the Sample solution

\(A_1\) = absorbance of the Standard solution

\(C_1\) = 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

\(M_{11}\) = molecular weight of rosuvastatin, 481.54

\(M_{12}\) = molecular weight of rosuvastatin calcium, 1001.14

Tolerances: NLT 80% (Q) of the labeled amount of rosuvastatin \((C_{22}H_{28}FN_{2}O_{9}S)\) is dissolved.

**Footnotes:**

- **Test 4:** If the product complies with this test, the labeling indicates that it meets Dissolution Test 4.
- **Medium:** 0.05 M sodium 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 10% w/v sodium citrate dihydrate solution or 10% w/v anhydrous citric acid solution to a pH of 6.6); 900 mL
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 rosuvastatin (C_{22}H_{35}FN_{2}O_{5}S) dissolved:

Result = \left( \frac{r_s}{r_U} \right) \times C_s \times V \times \frac{1}{L} \times \left[ M \times \left( \frac{M_s}{M_U} \right) \right] \times 100

<table>
<thead>
<tr>
<th>Flask Size</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>
</tbody>
</table>

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

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:

Result = \left( \frac{r_s}{r_U} \right) \times \left( \frac{C_s}{C_U} \right) \times \left[ M \times \left( \frac{M_s}{M_U} \right) \right] \times (1/F) \times 100

<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)</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Rosuvastatin ketone(^b)</td>
<td>1.6</td>
<td>0.71</td>
<td>2.1</td>
</tr>
<tr>
<td>Rosuvastatin lactone(^a)</td>
<td>2.3</td>
<td>1.0</td>
<td>1.5</td>
</tr>
<tr>
<td>Rosuvastatin ethyl ester (if present)(^a)</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>
</tbody>
</table>

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: Nominally 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 1

<table>
<thead>
<tr>
<th>Table 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>
</tbody>
</table>
Table 2 (continued)

<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>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>3.6</td>
</tr>
</tbody>
</table>

a (3RS,5RS,E)-7-[4-(4-Fluorophenyl)-6-isopropyl-2-(N-methylmethylsulfonamido)pyrimidin-5-yl]-3,3-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,E)-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-{[(E)-2-[(2S,4R)-4-hydroxy-6-oxotetrahydro-2H-pyran-2-yl]vinyl]-6-isopropylpyrimidin-2-yl]-N-methylmethanesulfonamide.

e Ethyl (3R,5S,E)-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

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