Atorvastatin Calcium Tablets

Type of Posting                      Revision Bulletin
Posting Date                        27–Apr–2018
Official Date                       01–May–2018
Expert Committee                    Chemical Medicines Monographs 2
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 Atorvastatin Calcium Tablets monograph. The purpose for the revision is to add **Dissolution Test 4** to accommodate drug products that were approved with different dissolution conditions and acceptance criteria.

- **Dissolution Test 4** was validated using the Inertsil ODS 3V brand of L1 packing column. The typical retention time for the atorvastatin peak is between 5.4 and 6.6 min.

Additionally, the acceptance criteria for the following two impurities in **Table 4** have been revised:

- Atorvastatin related compound D has been widened from NMT 0.35% to NMT 0.5%.
- Atorvastatin epoxy THF analog has been widened from NMT 0.25% to NMT 1.0%.

The Atorvastatin Calcium Tablets Revision Bulletin supersedes the monograph that will be official in *USP 41–NF 36*. The Revision Bulletin will be incorporated in *USP 42–NF 37*.

Should you have any questions, please contact Sujatha Ramakrishna, Principal Scientific Liaison (301-816-8349 or sxr@usp.org).
Add the following:

▲ Atorvastatin Calcium Tablets

**DEFINITION**

Atorvastatin Calcium Tablets contain an amount of atorvastatin calcium \([C_{27}H_{35}F_7NO_{15}Ca]\), equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin.

**IDENTIFICATION**

- **A.** The UV absorption spectrum of the major peak of the Sample solution corresponds to that 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**

- **PROEDURE**

  **Buffer:** 0.05 M ammonium citrate buffer pH 4.0 prepared as follows. Dissolve 9.62 g of anhydrous citric acid in 950 mL of water, adjust with ammonium hydroxide to a pH of 4.0, and dilute with water to 1000 mL.

  **Mobile phase:** Acetonitrile, stabilizer-free tetrahydrofuran, and Buffer (27:20:53).

  **Solution A:** Dissolve 9.62 g of anhydrous citric acid in 900 mL of water, adjust with ammonium hydroxide to a pH of 7.4, and dilute with water to 1000 mL.

  **Diluent:** Acetonitrile and Solution A (1:1).

  **System suitability solution:** 0.1 mg/mL of USP Atorvastatin Calcium RS and 0.01 mg/mL of USP Atorvastatin Related Compound H RS in Diluent. Shake mechanically for 30 min or until dissolved.

  **Standard solution:** 0.1 mg/mL of USP Atorvastatin Calcium RS in Diluent. Shake mechanically for 15 min or until dissolved.

  **Sample stock solution:** Prepare a known nominal concentration of atorvastatin by transferring NLT 10 Tablets to an appropriate volumetric flask. Add Diluent to about 50% of the final volume of the flask, and shake the mixture mechanically for 15 min or until dissolved. Dilute with Diluent to volume. Centrifuge or pass through a suitable filter of 0.45-µm pore size.

  **Sample solution:** Nominally equivalent to 0.1 mg/mL of atorvastatin in Diluent from the Sample stock solution.

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

  **Mode:** LC

  **Detector**
  - Assay: UV 244 nm
  - Identification A: Diode array; UV 200–400 nm

  **Column:** 4.6-mm x 25-cm; 5-µm packing L1

  **Column temperature:** 30°C

  **Flow rate:** 1.5 mL/min

  **Injection volume:** 20 µL

  **System suitability**

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

  **Suitability requirements**

  **Resolution:** NLT 5.0 between atorvastatin and atorvastatin related compound H; System suitability solution

  **Tailing factor:** NMT 1.5 for atorvastatin, System suitability solution

  **Relative standard deviation:** NMT 1.0%, Standard solution

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of atorvastatin \((C_{27}H_{35}F_7NO_{15}Ca)\) in the portion of Tablets taken:

  \[
  \text{Result} = \left( \frac{r_0}{r_S} \right) \times \left( \frac{C_i}{C_s} \right) \times \left[ M \times \left( \frac{M_{r1}}{M_{r2}} \right) \right] \times 100
  \]

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

  \(r_S\) = peak response of atorvastatin from the Standard solution.

  \(C_i\) = concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)

  \(C_s\) = concentration of USP Atorvastatin Calcium RS in the Sample solution (mg/mL)

  \(M\) = number of moles of atorvastatin per mole of atorvastatin calcium, 2

  \(M_{r1}\) = molecular weight of atorvastatin, 558.64

  \(M_{r2}\) = molecular weight of atorvastatin calcium, 1153.34

  **Acceptance criteria:** 94.5%–105.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Test 1**

  **Buffer:** 0.05 M phosphate buffer prepared as follows. Dissolve 6.8 g of monobasic potassium phosphate in 900 mL of water. Adjust with 6 N sodium hydroxide to a pH of 6.8 and dilute with water to 1 L.

  **Medium:** Buffer; 900 mL

  **Apparatus 2:** 75 rpm

  **Time:** 15 min

  **Diluent:** Acetonitrile and water (50:50).

  **Standard stock solution:** 1 mg/mL of USP Atorvastatin Calcium RS in Diluent. Shake mechanically for 10 min or until dissolved.

  **Standard solution:** \((L/900)\) mg/mL in Medium from Standard stock solution, where \(L\) is the label claim in mg/Tablet.

  **Sample solution:** Pass a portion of the solution under test through a suitable filter or centrifuge prior to analysis.

  **Instrumental conditions**
  (See Ultraviolet-Visible Spectroscopy (857).)

  **Mode:** UV

  **Analytical wavelength:** 244 nm

  **Cell:** See Table 1 or make appropriate dilutions of the solutions with Medium to be within the validated linearity range of the suitable spectrophotometer.

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Label Claim (mg/Tablet)</strong></td>
</tr>
<tr>
<td>10</td>
</tr>
<tr>
<td>20 and 40</td>
</tr>
<tr>
<td>80</td>
</tr>
</tbody>
</table>

  **Blank:** Medium

  **Analysis**

  **Samples:** Standard solution and Sample solution

  Calculate the percentage of the labeled amount of atorvastatin \((C_{27}H_{35}F_7NO_{15}Ca)\) dissolved:

  \[
  \left( \frac{A_u}{A_o} \right) \times C_i \times V \times D \times \left[ M \times \left( \frac{M_{r1}}{M_{r2}} \right) \right] \times (1/L) \times 100
  \]

  \(A_u\) = absorbance of the Sample solution.
2 Atorvastatin

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Official May 1, 2018

Table 2

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>0.69</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>0.74</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2.73</td>
<td>0</td>
<td>100</td>
</tr>
<tr>
<td>2.77</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>5.00</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

Medium: Solution C and Buffer (6:94); 900 mL
Apparatus 2: 75 rpm
Time: 30 min

Standard stock solution: 0.96 mg/mL of USP Atorvastatin Calcium RS in methanol

Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of atorvastatin (C_{33}H_{37}F_{2}N_{2}O_{5}) dissolved:

\[
\left(\frac{r_U}{r_S}\right) \times C_S \times V \times \left[\frac{M_U}{M_S}\right] \times \left[\frac{M_S}{M_U}\right] \times 100
\]

\(r_U\) = peak response of atorvastatin from the Sample solution
\(r_S\) = peak response of atorvastatin from the Standard solution
\(C_S\) = concentration of USP Atorvastatin Calcium RS in the Standard solution (mg/mL)
\(V\) = volume of Medium, 900 mL
\(M\) = number of moles of atorvastatin per mole of atorvastatin calcium, 2
\(M_{r1}\) = molecular weight of atorvastatin, 558.64
\(M_{r2}\) = molecular weight of atorvastatin calcium, 1155.34
\(L\) = label claim (mg/Tablet)

Suitability requirements

Sample: Standard solution

Apparatus 2: 75 rpm
Flow rate: 0.7 mL/min
Injection volume: 2 µL

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 1.5

Relative standard deviation: NMT 2.0%

Chromatographic system

Mode: LC
Detector: UV 248 nm

Column: 2.1-mm × 5-cm; 2.6-µm packing L1
Column temperature: 40°
Flow rate: 0.7 mL/min
Injection volume: 2 µL

System suitability

Sample: Standard solution

Suitability requirements

Tailing factor: NMT 2.0%

Relative standard deviation: NMT 2.0%

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C181417-M6340-CHM22015, rev. 00 20180427
Analysis

Samples: Standard solution and Sample solution

Calculate the percentage of the labeled amount of atorvastatin (C₃₃H₄₂F₄N₂O₂) dissolved:

\[ \left( \frac{r_0}{r_5} \right) C_0 \times V \times \left[ M \times \left( \frac{M_{11}}{M_{12}} \right) \right] \times (1/L) \times 100 \]

- **Uniformity of Dosage Units (905):** Meet the requirements

IMPURITIES

Change to read:

**Organic Impurities:**

Rinse glassware with Diluent before preparing solutions containing atorvastatin calcium.

 Buffer: 5.75 g/L of monobasic ammonium phosphate in water. Adjust with dilute acetic acid (10% v/v) or dilute ammonium hydroxide (10% v/v) to a pH of 4.3 ± 0.05.

 Solution A: Acetonitrile and stabilizer-free tetrahydrofuran (925:75)

 Solution B: Solution A and Buffer (42:58)

 Solution C: Methanol, Solution A, and Buffer (60:20:20)

 Diluent: N,N-Dimethylformamide

System suitability solution: 60 µg/mL of USP Atorvastatin Calcium RS, 50 µg/mL of USP Atorvastatin Related Compound B RS, 10 µg/mL of USP Atorvastatin Related Compound D RS in Diluent

Standard solution: 5 µg/mL of USP Atorvastatin Calcium RS in Diluent. Sonication may be necessary for complete dissolution.

Sample solution: Nominally equivalent to 1 mg/mL of atorvastatin, prepared as follows. Crush and finely powder NLT 20 Tablets. Transfer the amount of powder, equivalent to about 30 mg of atorvastatin, to a 50-mL volumetric flask. Add 30 mL of Diluent and shake mechanically for 15 min. Dilute with Diluent to volume and pass the solution through a suitable filter of 0.45-µm pore size, discarding the first few mL of the filtrate.

Mobile phase: See Table 3.

| Table 3 |
|---|---|---|---|
| Time (min) | Solution B (%) | Solution C (%) | Flow Rate (mL/min) |
| 0 | 100 | 0 | 1.8 |
| 30 | 100 | 0 | 1.8 |
| 45 | 25 | 75 | 1.5 |

Table 3 (continued)

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution B (%)</th>
<th>Solution C (%)</th>
<th>Flow Rate (mL/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>50</td>
<td>25</td>
<td>75</td>
<td>1.5</td>
</tr>
<tr>
<td>55</td>
<td>20</td>
<td>80</td>
<td>1.5</td>
</tr>
<tr>
<td>58</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
<tr>
<td>65</td>
<td>100</td>
<td>0</td>
<td>1.8</td>
</tr>
</tbody>
</table>

For the Standard solution, the run time is only 30 min. For the System suitability solution and Sample solution, the run time is 65 min.

Chromatographic system

(See Chromatography (621), System Suitability.)

Mode: LC

Detector: UV 244 nm

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: See Table 3.

Injection volume: 20 µL

System suitability

Sample: System suitability solution

[NOTE—The relative retention times of all peaks eluting before atorvastatin related compound H are calculated with respect to the atorvastatin peak. The relative retention times for all peaks eluting after atorvastatin related compound H are calculated with respect to atorvastatin related compound H.]

Suitability requirements

Resolution: NLT 1.4 between atorvastatin related compound B and atorvastatin

Tailing factor: NMT 1.5 for the atorvastatin peak

Relative standard deviation: NMT 5% for the atorvastatin peak

Signal-to-noise ratio: NLT 10 for atorvastatin related compound D

Analysis

Samples: Standard solution and Sample solution

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

Result = \( \left( \frac{r_0}{r_5} \right) C_0 \times V \times \left[ M \times \left( \frac{M_{11}}{M_{12}} \right) \times (1/L) \times 100 \right] \)

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

\( r_5 = \) peak response of atorvastatin from the Sample solution

\( C_0 = \) concentration of USP Atorvastatin Calcium RS in the Sample solution (mg/mL)

\( C_0 = \) nominal concentration of atorvastatin in the Sample solution (mg/mL)

\( M = \) number of moles of atorvastatin per mole of atorvastatin calcium, 2

\( M_{11} = \) molecular weight of atorvastatin, 558.64

\( M_{12} = \) molecular weight of atorvastatin calcium, 1155.34

\( F = \) relative response factor (see Table 4)

Acceptance criteria: See Table 4.

Table 4

<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>Atorvastatin amide</td>
<td>0.44</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Atorvastatin

Table 4 (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>Atorvastatin related compound A&lt;sup&gt;a,c&lt;/sup&gt;</td>
<td>0.84</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone analog&lt;sup&gt;d&lt;/sup&gt;</td>
<td>0.88</td>
<td>0.68</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin related compound B&lt;sup&gt;b,c&lt;/sup&gt;</td>
<td>0.94</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>1.00</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound C&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1.09</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone lactone&lt;sup&gt;h,g&lt;/sup&gt;</td>
<td>1.62</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound H&lt;sup&gt;f&lt;/sup&gt;</td>
<td>1.00</td>
<td>1.18</td>
<td>1.0</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone oxazin analog&lt;sup&gt;i&lt;/sup&gt;</td>
<td>1.06</td>
<td>0.53</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin methyl ester&lt;sup&gt;h,i&lt;/sup&gt;</td>
<td>1.12</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone oxazin 7-hydroxy analog, if present&lt;sup&gt;j&lt;/sup&gt;</td>
<td>1.14</td>
<td>0.53</td>
<td>0.5</td>
</tr>
<tr>
<td>Atorvastatin pyrrolidone oxazin analog&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1.20</td>
<td>1.12</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin related compound D&lt;sup&gt;j&lt;/sup&gt;</td>
<td>1.27</td>
<td>1.12</td>
<td>—</td>
</tr>
<tr>
<td>Atorvastatin tert-butyl ester&lt;sup&gt;k&lt;/sup&gt;</td>
<td>1.49</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Any other unspecified degradation product</td>
<td>—</td>
<td>1.00</td>
<td>0.2</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
<td>—</td>
<td>4.0</td>
</tr>
</tbody>
</table>

<sup>a</sup> (3R,5R)-7-{(3R,5S)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-isopropyl-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl]-3,5-dihydroxyheptanoic acid.
<sup>b</sup> Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.
<sup>c</sup> (3R,5R)-7-{(3R,5S)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-isopropyl-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl]-3,5-dihydroxyheptanoic acid.
<sup>d</sup> Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.
<sup>e</sup> (3R,5R)-7-{(3R,5S)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-isopropyl-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl]-3,5-dihydroxyheptanoic acid.
<sup>f</sup> (3R,5R)-7-{(3R,5S)-7-[2-(4-Fluorophenyl)-5-isopropyl-3-isopropyl-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl]-3,5-dihydroxyheptanoic acid.
<sup>g</sup> (3R,5S)-7-{(3R,5S)-7-[2-(4-Fluorophenyl)-4-hydroxy-6-oxotetrahydro-2H-pyrrl-2-yl]ethyl}-3-isopropyl-2-oxo-N,4-diphenyl-3,5-dihydroxyheptanoic acid.
<sup>h</sup> 5-(4-Fluorophenyl)-1-{(2R,4R)-4-hydroxy-6-oxotetrahydro-2H-pyrrl-2-yl}ethyl)-2-isopropyl-N,4-diphenyl-3-carboxamide.
<sup>i</sup> 4-(1b-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8a-isopropyl-7-phenyl-8-(phenylcarbamoyl)hexahydro-2H-pyrrl[2,1-b][1,3]oxazin-2-yl)-3-hydroxybutanoic acid.
<sup>j</sup> (3R,5S)-Methyl 7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl)-3,5-dihydroxyheptanoate.
<sup>k</sup> (3R)-4-(1b-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1-a-phenyl-7a-(phenylcarbamoyl)hexahydro-1aH-oxireno[2′,3′:3,4]pyropyrrl[2,1-b][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.
<sup>l</sup> 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-N,N,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.
<sup>m</sup> Atorvastatin related compound D can undergo transformation equilibrium to the atorvastatin epoxy THF analog. The equilibrium can be shifted under slightly acidic conditions and therefore some products could have a combined specification reported under atorvastatin related compound D.
<sup>n</sup> 3-(4-Fluorobenzoyl)-2-isobutyryl-N,N,3-diphenyloxirane-2-carboxamide.
<sup>o</sup> (3R,5S)-tert-Butyl 7-(2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl)-3,5-dihydroxyheptanoate.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.
- **LABELING:** When more than one Dissolution test is given, the labeling states the test used, only if Test 1 is not used.
- **USP REFERENCE STANDARDS (11)**

**USP Atorvastatin Calcium RS**

**USP Atorvastatin Related Compound B RS**

Calcium (3S,5R)-7-{[2-(4-Fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1H-pyrrl-1-yl]-3,5-dihydroxyheptanoate (1:1). Ca<sub>6</sub>H<sub>12</sub>F<sub>2</sub>N<sub>2</sub>O<sub>10</sub> 1155.34

**USP Atorvastatin Related Compound D RS**

3-(4-Fluorobenzoyl)-2-isobutyryl-N,3-diphenyloxirane-2-carboxamide.

Ca<sub>2</sub>H<sub>2</sub>FNO<sub>4</sub> 431.46

**USP Atorvastatin Related Compound H RS**

5-(4-Fluorophenyl)-1-{[2R,4R]-4-hydroxy-6-oxotetrahydro-2H-pyrrl-2-yl}ethyl)-2-isopropyl-N,4-diphenyl-1H-pyrrl-3-carboxamide.

C<sub>26</sub>H<sub>25</sub>FNO<sub>4</sub> 540.62

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