Olmesartan Medoxomil Tablets

Type of Posting: Notice of Intent to Revise
Posting Date: 26–July–2019
Targeted Official Date: To Be Determined, Revision Bulletin
Expert Committee: Chemical Medicines Monographs 2

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 2 Expert Committee intends to revise the Olmesartan Medoxomil Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 5.

- The analytical procedure in Dissolution Test 5 was validated using a Kromasil C18 brand of L1 column from Akzo Nobel Separations. The typical retention time for olmesartan medoximil is about 2.2 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 Donald Min, Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@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.
Olmesartan Medoxomil Tablets

**DEFINITION**
Olmesartan Medoxomil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{3}).

**IDENTIFICATION**
- **A.** The UV absorption spectra of the major 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**
  - **Solution A:** 3.1 g/L of formic acid
  - **Solution B:** Acetonitrile and Solution A (10:90)
  - **Solution C:** Acetonitrile and Solution A (90:10)
  - **Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution B (%)</th>
<th>Solution C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68.8</td>
<td>31.2</td>
</tr>
<tr>
<td>1.5</td>
<td>37.5</td>
<td>62.5</td>
</tr>
<tr>
<td>1.6</td>
<td>68.8</td>
<td>31.2</td>
</tr>
<tr>
<td>3.0</td>
<td>68.8</td>
<td>31.2</td>
</tr>
</tbody>
</table>

Diluent: Acetonitrile and water (60:40)

**Standard solution:** 40 µg/mL of USP Olmesartan Medoxomil RS in Diluent

**Sample stock solution:** Prepare solutions of nominal concentrations of olmesartan medoxomil in Diluent as follows. To NLT 10 Tablets for 5- and 20-mg Tablet strengths and NLT 5 Tablets for 40-mg Tablet strength in a 200-mL volumetric flask, add Diluent to volume. Sonicate with occasional shaking to disintegrate the Tablets completely, centrifuge the suspension, and use the supernatant.

**Sample solution:** Nominally 40 µg/mL of olmesartan medoxomil in Diluent from Sample stock solution

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

**Mode:** LC

**Detector:** UV 249 nm. For Identification A, use a diode array detector in the range of 200–400 nm.

**Column:** 2.1-mm × 5-cm; 1.7-µm packing L1

**Column temperature:** 35°C

**Flow rate:** 0.6 mL/min

**Injection volume:** 1 µL

**System suitability**
- **Sample:** Standard solution
- **Suitability requirements**
  - **Tailing factor:** NMT 2.0
  - **Relative standard deviation:** NMT 1.0%

**Analysis**
- **Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{3}) in the portion of Tablets taken:

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

- \( r_u \) = peak response of olmesartan medoxomil from the Sample solution
- \( r_s \) = peak response of olmesartan medoxomil from the Standard solution
- \( C_s \) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (µg/mL)
- \( C_u \) = nominal concentration of olmesartan medoxomil in the Sample solution (µg/mL)

**Acceptance criteria:** 90.0%–110.0%

**PERFORMANCE TESTS**

**Change to read:**

- **Dissolution (711)**

  **Test 1**
  - **Medium:** pH 6.8 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions)
  - **For Tablets labeled to contain 5 mg:** 500 mL
  - **For Tablets labeled to contain 20 and 40 mg:** 1000 mL
  - **Apparatus 2:** 50 rpm
  - **Time:** 30 min
  - **Diluent:** Acetonitrile and water (60:40)
  - **Standard stock solution:** 2 mg/mL of USP Olmesartan Medoxomil RS in Diluent
  - **Standard solution:** \((L/V)\) mg/mL of USP Olmesartan Medoxomil RS in Medium, where \(L\) is the label claim in mg/Tablet and \(V\) is the volume of the Medium in mL from the Standard stock solution
  - **Sample solution:** Pass a portion of the solution under test through a glass fiber filter of 1.2-µm pore size.

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

  **Mode:** UV

  **Analytical wavelength:** 258 nm

  **Cells**
  - For Tablets labeled to contain 5 and 20 mg: 1 cm
  - For Tablets labeled to contain 40 mg: 0.5 cm
  - **Blank:** Medium

  **Analysis**
  - **Samples:** Standard solution and Sample solution
  
  Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{3}) dissolved:
  
  \[ \text{Result} = \left( \frac{A_u}{A_s} \right) \times \frac{C_s}{V} \times (1/L) \times 100 \]

  - \( A_u \) = absorbance of the Sample solution
  - \( A_s \) = absorbance of the Standard solution
  - \( C_s \) = concentration of the Standard solution (mg/mL)
  - \( V \) = volume of Medium (see Medium)
  - \( L \) = label claim (mg/Tablet)

  **Tolerances:** NLT 75% (Q) of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{6}O_{3}) is dissolved.

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

  **Medium:** pH 7.2 phosphate buffer (see Reagents, Indicators, and Solutions—Buffer Solutions), 900 mL

  **Apparatus 2:** 75 rpm

  **Time:** 30 min

  **Standard stock solution:** 0.2 mg/mL of USP Olmesartan Medoxomil RS prepared as follows. Transfer an appropriate amount of USP Olmesartan Medoxomil RS into a suitable volumetric flask. Dissolve in 30% of the flask volume of acetonitrile. Dilute with Medium to volume and mix.
Olmesartan

Standard solution: (L/1000) mg/mL of USP Olmesartan Medoxomil RS in Medium, from the 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 of 0.45-µm pore size and discard the first few milliliters of the filtrate.

Instrumental conditions
Mode: UV
Analytical wavelength: 257 nm
Cell: 1 cm
Blank: Medium

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of olmesartan medoxomil (C₁₂H₁₈N₂O₅) dissolved:

\[
\text{Result} = \left(\frac{A_i}{A_f}\right) \times \frac{C_i \times V \times (1/L) \times 100}{L}
\]

where \(A_i\) = absorbance of the Sample solution, \(A_f\) = absorbance of the Standard solution, \(C_i\) = concentration of the Standard solution (mg/mL), \(V\) = volume of Medium, 900 mL, and \(L\) = label claim (mg/Tablet).

Tolerances: NLT 80% (Q) of the labeled amount of olmesartan medoxomil (C₁₂H₁₈N₂O₅) is dissolved.

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

Medium: 0.05 M hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 45 min
Buffer: 1.36 g/L of monobasic potassium phosphate in water. Adjust with phosphoric acid to a pH of 2.5.
Solution A: Acetonitrile and Buffer (20:80)
Solution B: Acetonitrile and Buffer (80:20)
Mobile phase: See Table 2.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>4.0</td>
<td>52</td>
<td>48</td>
</tr>
<tr>
<td>5.0</td>
<td>75</td>
<td>25</td>
</tr>
<tr>
<td>7.0</td>
<td>75</td>
<td>25</td>
</tr>
</tbody>
</table>

Diluent A: Acetonitrile, water, and phosphoric acid (50:50:2)
Diluent B: Medium and Diluent A (50:50)

Standard stock solution: 0.22 mg/mL of USP Olmesartan Medoxomil RS in Diluent A, prepared as follows. Transfer an appropriate amount of USP Olmesartan Medoxomil RS to a suitable volumetric flask. Add Diluent A to 60% of the total volume and sonicate to dissolve. Dilute with Diluent A to volume and mix well.

Standard solution
For Tablets labeled to contain 5 mg: 2.75 µg/mL of USP Olmesartan Medoxomil RS in Diluent B from the Standard stock solution
For Tablets labeled to contain 20 mg: 11 µg/mL of USP Olmesartan Medoxomil RS in Diluent B from the Standard stock solution
For Tablets labeled to contain 40 mg: 22 µg/mL of USP Olmesartan Medoxomil RS in Diluent B 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 and discard the first few milliliters of the filtrate. Transfer 5 mL of the filtered test solution to a 10-mL volumetric flask and dilute with Diluent A to volume.

Chromatographic system
(See Chromatography (621), System Suitability.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Temperatures
Autosampler: 5°C
Column: 30°C
Injection rate: 1.5 mL/min
Injection volume: 10 µL

System suitability
Sample: Standard solution
[NOTE—The relative retention times for olmesartan and olmesartan medoxomil are 0.45 and 1.00, respectively.]
Suitability requirements
Tailing factor: NMT 2.0 for olmesartan medoxomil
Relative standard deviation: NMT 2.0% for olmesartan medoxomil

Analysis
Samples: Standard solution and Sample solution
Calculate the concentration (C₃) of olmesartan medoxomil (C₁₂H₁₈N₂O₅) in the Sample solution:

\[
\text{Result} = \left(\frac{r_1}{r_2}\right) \times C_3
\]

where \(r_1\) = peak response of olmesartan medoxomil from the Sample solution, \(r_2\) = peak response of olmesartan medoxomil from the Standard solution, \(C_3\) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL).

Calculate the concentration (C₄) of olmesartan as olmesartan medoxomil (C₁₂H₁₈N₂O₅) in the Sample solution:

\[
\text{Result} = \left(\frac{r_1}{r_2}\right) \times C_4
\]

where \(r_1\) = peak response of olmesartan from the Sample solution, \(r_2\) = peak response of olmesartan medoxomil from the Standard solution, \(C_4\) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL), \(F\) = relative response factor, 0.88, \(M_{r2}\) = molecular weight of olmesartan medoxomil, 558.59, and \(M_{r1}\) = molecular weight of olmesartan, 446.50.

Calculate the percentage of the labeled amount of olmesartan medoxomil (C₁₂H₁₈N₂O₅) dissolved:

\[
\text{Result} = \left(\frac{[C_4 + C_5]}{[D] \times V \times (1/L) \times 100}
\]

where \(C_4\) = concentration of olmesartan medoxomil in the Sample solution (mg/mL), \(C_5\) = concentration of olmesartan as olmesartan medoxomil in the Sample solution (mg/mL), \(D\) = dilution factor for the Sample solution, \(V\) = volume of Medium, 900 mL.
Tolerances: NLT 75% (Q) of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{2}O_{4}) is dissolved.

**Test 5:** If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 5.

**Medium:** pH 6.8 phosphate buffer (Dissolve 68.0 g of monobasic potassium phosphate in 8000 mL of water in a suitable container. Adjust with diluted sodium hydroxide to a pH of 6.8 ± 0.05. Dilute with water to 10,000 mL). 900 mL. [NOTE—Tight control of the pH is critical.]

**Apparatus:** 50 rpm. Use peak vessels.

**Time:** 30 min

**Buffer:** Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water. Add 5 mL of triethylamine and mix. Adjust with phosphoric acid to a pH of 2.5.

**Mobile phase:** Acetonitrile and water (60:40)

**Diluent:** Acetonitrile and Medium (50:50)

**Standard stock solution:** 0.222 mg/mL of USP Olmesartan Medoxomil RS in Diluent. Sonication may be needed to dissolve.

**Standard solution**

[NOTE—Preserve at 2°–8° after preparation.]

**For Tablets labeled to contain 5 mg:** 5.5 µg/mL of USP Olmesartan Medoxomil RS in Medium from the Standard stock solution

**For Tablets labeled to contain 20 mg:** 22 µg/mL of USP Olmesartan Medoxomil RS in Medium from the Standard stock solution

**For Tablets labeled to contain 40 mg:** 44 µg/mL of USP Olmesartan Medoxomil 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 and discard the first 1 mL of the filtrate. [NOTE—Preserve immediately at 2°–8° after preparation.]

**Chromatographic system**

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 250 nm

**Column:** 4.0-mm × 12.5-cm; 5-µm packing L1

**Temperatures**

- Autosampler: 8°
- Column: 40°
- Flow rate: 1.5 mL/min
- Injection volume: 10 µL

**System suitability**

**Sample:** Standard solution

**Suitability requirements**

- Tailing factor: 0.8–1.5 for olmesartan medoxomil
- Relative standard deviation: NMT 2.0% for the sum of the peak responses of olmesartan and olmesartan medoxomil

**Analysis**

**Samples:** Standard solution and Sample solution

Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{2}O_{4}) dissolved:

\[
\text{Result} = \left( \frac{r_{U}}{r_{S}} \right) \times C_{S} \times V \times \left( \frac{1}{L} \right) \times 100
\]

- \(r_{U}\) = sum of the peak responses of olmesartan and olmesartan medoxomil from the Sample solution
- \(r_{S}\) = sum of the peak responses of olmesartan and olmesartan medoxomil from the Standard solution
- \(C_{S}\) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
- \(V\) = volume of Medium, 900 mL
- \(L\) = label claim of olmesartan medoxomil (mg/Tablet)

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\[ C_i = \text{concentration of USP Olmesartan} \]

\[ D = \text{dilution factor of the Sample solution} \]

\[ V = \text{volume of Medium, 900 mL} \]

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

Tolerances: NLT 80% (Q) of the labeled amount of olmesartan medoxomil (C\text{H}_{30}\text{N}_6\text{O}_6) is dissolved.

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

**Impurities**

• **Organic Impurities**

  **Buffer:** 0.015 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.5.

  **Solution A:** Acetonitrile and Buffer (20:80)

  **Solution B:** Acetonitrile and Buffer (79:21)

**Mobile phase:** See Table 3.

**System suitability**

- **Suitability requirements**
  - **System suitability solution:**
    - **Diluent:** Acetonitrile and water (90:10)
    - **System suitability solution:**
    - **Sample solution:** Nominally 1 mg/mL of olmesartan
  - **Mobile phase:**
    - **Solution A:** Acetonitrile and 0.015 M monobasic potassium phosphate. Adjust with phosphoric acid to a pH of 3.5.
    - **Solution B:** Acetonitrile and 79:21 (79:21) Buffer

**Chromatographic system**

- **Column:** 4.6-mm × 10-cm; 3.5-µm packing L7
- **Column temperature:** 40°C
- **Flow rate:** 1 mL/min
- **Injection volume:** 10 µL

**Samples**:

- **System suitability solution** and **Sensitivity solution**

**Analysis**

**Samples:** **Standard solution** and **Sample solution**

Calculate the percentage of each degradation product in the portion of Tablets taken:

\[
\text{Result} = (r_i/r_o) \times (C_i/C_o) \times (1/F) \times 100
\]

- **r_i** = peak response of each degradation product from the **Sample solution**
- **r_o** = peak response of olmesartan medoxomil from the **Standard solution**
- **C_i** = concentration of in the **Standard solution** (mg/mL)
- **C_o** = nominal concentration of olmesartan medoxomil in the **Sample solution** (mg/mL)
- **F** = relative response factor (see Table 4)

**Acceptance criteria:** See Table 4. Disregard peaks below 0.1%.

**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>Olmesartan</td>
<td>0.2</td>
<td>1.0</td>
<td>2.5</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A(^b)</td>
<td>0.7</td>
<td>1.6</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan dimer(^c)</td>
<td>1.2</td>
<td>0.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Olefinic impurity(^d)</td>
<td>1.5</td>
<td>1.0</td>
<td>0.6</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>4.1</td>
</tr>
</tbody>
</table>

\(^a\) 1-[\((2'-(1'H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-(2-hydroxyprop-2-yl)-2-propyl-1'H-imidazole-5-carboxylic acid.

\(^b\) This is a process-related impurity that is controlled in the drug substance.

\(^c\) 1-[\((2'-(1'H-Tetrazol-5-yl)-1',1'-biphenyl)-4-yl)methyl]-4-(2-[\((2'-(1'H-tetrazol-5-yl)-1',1'-biphenyl)-4-yl)methyl]-4-(2-hydroxyprop-2-yl)-2-propyl-1'H-imidazole-5-carboxylic acid.

\(^d\) [(5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl]-1-(2'-(1'H-tetrazol-5-yl)biphenyl-4-yl)methyl]-4-(prop-1-en-2-yl)-2-propyl-1'H-imidazole-5-carboxylate.

**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 Olmesartan Medoxomil RS

  USP Olmesartan Medoxomil Related Compound A RS

  1-[\((2'-(1'H-Tetrazol-5-yl)biphenyl-4-yl)methyl]-4-dimethyl-2-propyl-1'H-furo[3,4-d]imidazol-6(4H)-one.

  C\text{H}_{26}\text{N}_{10}\text{O}_5 428.49

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