Olmesartan Medoxomil Tablets

Type of Posting      Revision Bulletin
Posting Date        26–Oct–2018
Official Date       01–Nov–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 Olmesartan Medoxomil Tablets monograph. The purpose for the revision is to widen the acceptance criteria for the Definition and Assay of olmesartan medoxomil from NLT 93.0% and NMT 105.0% to NLT 90.0% and NMT 110.0% based on the manufacturers’ FDA-approved drug product specifications and to add Dissolution Test 3 to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- Dissolution Test 3 was validated using a Zorbax Rx C8 brand of L7 column. The typical retention time for olmesartan medoxomil is about 3.8 min.

The revision also necessitates a change in the table numbering in the Organic Impurities test.

The Olmesartan Medoxomil Tablets Revision Bulletin supersedes the currently official monograph.

Should you have any questions, please contact Donald Min, Senior Scientific Liaison (301-230-7457 or ddm@usp.org) or Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).
Olmesartan Medoxomil Tablets

Change to read:

DEFINITION
Olmesartan Medoxomil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil (C_{31}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

Change to read:

• 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>66.8</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>66.8</td>
<td>31.2</td>
</tr>
<tr>
<td>3.0</td>
<td>66.8</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_{31}H_{30}N_{6}O_{3}) in the portion of Tablets taken:

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

where
- \( r_u \): 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_{31}H_{30}N_{6}O_{3}) dissolved:

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

where
- \( A_s \): absorbance of the Sample solution
- \( A_i \): 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_{31}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

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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.

**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:** LC
- **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 \((C_{29}H_{30}N_{6}O_{6}\)) dissolved:
    \[
    \text{Result} = \left( \frac{A_i}{A_s} \right) \times C_i \times V \times \left( \frac{1}{L} \right) \times 100
    \]
  - \(A_i\) = absorbance of the Sample solution
  - \(A_s\) = absorbance of the Standard solution
  - \(C_i\) = concentration of the Standard solution (mg/mL)
  - \(V\) = volume of Medium, 900 mL
  - \(L\) = label claim (mg/Tablet)

**Tolerances:** NLT 80% (Q) of the labeled amount of olmesartan medoxomil \((C_{29}H_{30}N_{6}O_{6}\)) 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 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**
- **Mode:** LC
- **Detector:** UV 250 nm
- **Column:** 4.6-mm × 15-cm; 5-μm packing L7
- **Temperatures**
  - **Autosampler:** 5°
  - **Column:** 30°
- **Flow 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 \((C_i)\) of olmesartan medoxomil \((C_{29}H_{30}N_{6}O_{6}\)) in the Sample solution:
  \[
  \text{Result} = \left( \frac{r_i}{r_s} \right) \times C_i
  \]
  - \(r_i\) = peak response of olmesartan medoxomil from the Sample solution
  - \(r_s\) = peak response of olmesartan medoxomil from the Standard solution
  - \(C_i\) = concentration of USP Olmesartan Medoxomil RS in the **Standard solution** (mg/mL)

- Calculate the concentration \((C_i)\) of olmesartan as olmesartan medoxomil \((C_{29}H_{30}N_{6}O_{6}\)) in the Sample solution:
  \[
  \text{Result} = \left( \frac{r_i}{r_s} \right) \times C_i \times (1/1) \times (M_i/M_s)
  \]
  - \(r_i\) = peak response of olmesartan from the Sample solution
  - \(r_s\) = peak response of olmesartan from the Standard solution
  - \(C_i\) = concentration of USP Olmesartan Medoxomil RS in the **Standard solution** (mg/mL)
  - \(M_i\) = molecular weight of olmesartan medoxomil, 558.59
  - \(M_s\) = molecular weight of olmesartan, 446.50

- Calculate the percentage of the labeled amount of olmesartan medoxomil \((C_{29}H_{30}N_{6}O_{6}\)) dissolved:
  \[
  \text{Result} = \left( \frac{C_i + C_s}{D} \right) \times V \times (1/L) \times 100
  \]
= concentration of olmesartan medoxomil in the Sample solution (mg/mL)

\( C_2 \) = 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

\( L \) = label claim for olmesartan medoxomil (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of olmesartan medoxomil \( (C_{29}H_{30}N_6O_4) \) is dissolved.

- **UNIFORMITY OF DOSAGE UNITS** (905): Meet the requirements

### IMPURITIES

**Change to read:**

- **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.

  **Diluent:** Acetonitrile and water (90:10)

**System suitability solution:** 0.01 mg/mL of USP Olmesartan Medoxomil RS in Diluent

**Sensitivity solution:** 0.002 mg/mL of USP Olmesartan Medoxomil RS in Diluent from the Standard solution

**Sample solution:** Nominally 1 mg/mL of olmesartan medoxomil in Diluent prepared as follows. Dissolve a suitable number of Tablets in Diluent. Sonicate and/or shake occasionally to disintegrate the Tablets completely. Centrifuge and pass the supernatant through a suitable filter of 0.45-µm pore size.

### Chromatographic system

(See Chromatography (621), System Suitability.)

**Mode:** LC

**Detector:** UV 250 nm

**Column:** 4.6-mm x 10-cm; 3.5-µm packing L7

**Column temperature:** 40°C

**Flow rate:** 1 mL/min

**Injection volume:** 10 µL

**System suitability**

**Samples:** System suitability solution and Sensitivity solution

**Suitability requirements**

**Resolution:** NLT 5 between olmesartan medoxomil and olmesartan medoxomil related compound A, System suitability solution

**Relative standard deviation:** NMT 2.0% for both peaks, System suitability solution

### Signal-to-noise ratio: NLT 30, Sensitivity solution

**Analysis**

**Samples:** Standard solution and Sample solution

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

\[ \text{Result} = (r_C/r_u) \times (C_0/C_u) \times (1/F) \times 100 \]

\( r_C \) = peak response of each degradation product from the Sample solution

\( r_u \) = peak response of olmesartan medoxomil from the Standard solution

\( C_0 \) = concentration of in the Standard solution (mg/mL)

\( C_u \) = 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>
<thead>
<tr>
<th>Table 3</th>
<th>(RB 1-Nov-2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (min)</td>
<td>Solution A (%)</td>
</tr>
<tr>
<td>0</td>
<td>75</td>
</tr>
<tr>
<td>10</td>
<td>75</td>
</tr>
<tr>
<td>35</td>
<td>0</td>
</tr>
<tr>
<td>45</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Table 4</th>
<th>(RB 1-Nov-2018)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name</td>
<td>Relative Retention Time</td>
</tr>
<tr>
<td>Olmesartan</td>
<td>0.2</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A</td>
<td>0.7</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
</tr>
<tr>
<td>Olmesartan dimer</td>
<td>1.2</td>
</tr>
<tr>
<td>Olefinic impurity</td>
<td>1.5</td>
</tr>
<tr>
<td>Any unspecified degradation product</td>
<td>—</td>
</tr>
<tr>
<td>Total degradation products</td>
<td>—</td>
</tr>
</tbody>
</table>

\( ^a \)-1-(2’-(1H-Tetrazol-5-yl)biphenyl-4-yl)(methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.

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

\( ^c \)-1-(2’-(1H-Tetrazol-5-yl)-1’,1’-biphenyl-4-yl)(methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.

\( ^d \)(S-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 1-(2’-(1H-tetrazol-5-yl)biphenyl-4-yl)(methyl)-4-(2-propyl-1-ent-2-yl)-2-propyl-1H-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’-(1H-Tetrazol-5-yl)biphenyl-4-yl)(methyl)-4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4H)-one.\( \text{C}_{28}\text{H}_{32}\text{N}_6\text{O}_8 \) 428.49

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