Amlodipine and Olmesartan Medoxomil Tablets

Type of Posting  Revision Bulletin
Posting Date  28–Feb–2020
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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 Amlodipine and Olmesartan Medoxomil Tablets monograph. The purpose for the revision is to add Dissolution Test 2 to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests. Labeling information has been incorporated to support the inclusion of Dissolution Test 2. This revision also necessitates a change in the table numbering in the test for Organic Impurities.

- Dissolution Test 2 was validated using a GL Sciences Inertsil ODS-3 brand of L1 column. The typical retention time for olmesartan medoxomil is about 5.4 min.

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

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

DEFINITION
Amlodipine and Olmesartan Medoxomil Tablets contain an amount of Amlodipine Besylate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine \((\text{C}_{20}\text{H}_{12}\text{ClN}_{2}\text{O}_3)\) and NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil \((\text{C}_{25}\text{H}_{18}\text{N}_{4}\text{O}_3)\).

IDENTIFICATION
• **A.** The UV spectra of the amlodipine and olmesartan medoxomil peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.
• **B.** The retention times of the amlodipine and olmesartan medoxomil peaks of the Sample solution correspond to those of the Standard solution, as obtained in the Assay.

ASSAY
**PROCEDURE**
**Solution A:** 6.9 g/L of sodium phosphate, monobasic. Adjust with phosphoric acid to a pH of 2.5.

**Solution B:** Acetonitrile

**Mobile phase:** See Table 1.

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

**Standard stock solution:** 0.28 mg/mL of USP Amlodipine Besylate RS and 0.8 mg/mL of USP Olmesartan Medoxomil RS in Diluent

**Standard solution:** 0.056 mg/mL of USP Amlodipine Besylate RS and 0.16 mg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution

**Sample stock solution:** Nominal concentrations given in Table 2 are prepared as follows.

For Tablet strength 5/20, transfer NLT 5 Tablets equivalent to 25 mg of amlodipine and 100 mg of olmesartan medoxomil into a suitable volumetric flask. Add water to 20% of the total volume and sonicate for 5 min. Add acetonitrile to 20% of the total volume and sonicate for 5 min. Add Diluent to 30% of the total volume and sonicate for 15 min. Dilute with Diluent to volume. Centrifuge a portion of the solution for 10 min and pass through a filter of 0.45-µm pore size.

For Tablet strength 5/40, 10/20, or 10/40, transfer NLT 5 Tablets equivalent to 25 mg of amlodipine and 200 mg of olmesartan medoxomil, 50 mg of amlodipine and 100 mg of olmesartan medoxomil, or 50 mg of amlodipine and 200 mg of olmesartan medoxomil into a suitable volumetric flask. Add water to 10% of the total volume and sonicate for 5 min. Add acetonitrile to 10% of the total volume and sonicate for 5 min. Add Diluent to 30% of the total volume and sonicate for 15 min. Dilute with Diluent to volume. Centrifuge a portion of the solution for 10 min and pass through a filter of 0.45-µm pore size.

**Mobile phase:** See Table 1.

<table>
<thead>
<tr>
<th>Time (min)</th>
<th>Solution A (%)</th>
<th>Solution B (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>12</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>15</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>21</td>
<td>30</td>
<td>70</td>
</tr>
<tr>
<td>23</td>
<td>68</td>
<td>32</td>
</tr>
<tr>
<td>25</td>
<td>68</td>
<td>32</td>
</tr>
</tbody>
</table>

**Table 1**

**Table 2**

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20, 10/40</td>
<td>0.5</td>
<td>2</td>
</tr>
<tr>
<td>5/40</td>
<td>0.25</td>
<td>2</td>
</tr>
<tr>
<td>10/20</td>
<td>0.5</td>
<td>1</td>
</tr>
</tbody>
</table>

**Sample solution:** Nominal concentrations in Diluent from Sample stock solution are given in Table 3.

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20, 10/40</td>
<td>0.04</td>
<td>0.16</td>
</tr>
<tr>
<td>5/40</td>
<td>0.02</td>
<td>0.16</td>
</tr>
<tr>
<td>10/20</td>
<td>0.04</td>
<td>0.08</td>
</tr>
</tbody>
</table>

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

**Mode:** LC

**Detector:** UV 254 nm. For Identification A, use a diode array detector in the range of 200–400 nm.

**Column:** 4.6-mm × 25-cm; 5-µm packing L11

**Temperatures**
- Autosampler: 5°
- Column: 60°

**Flow rate:** 2 mL/min

**Injection volume:** 10 µL

**System suitability**
**Sample:** Standard solution

**Suitability requirements**
- **Tailing factor:** NMT 2.0 for amlodipine and olmesartan medoxomil peaks
- **Relative standard deviation:** NMT 2.0% for amlodipine and olmesartan medoxomil peaks

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

Calculate the percentage of the labeled amount of amlodipine \((\text{C}_{20}\text{H}_{12}\text{ClN}_{2}\text{O}_3)\) in the portion of Tablets taken:

\[
\text{Result} = \left(\frac{r_0}{r_s}\right) \times \left(\frac{C_0}{C_s}\right) = \left(\frac{M_1}{M_2}\right) \times 100
\]

where:
- \(r_0\) = peak response of amlodipine from the Sample solution
- \(r_s\) = peak response of amlodipine from the Standard solution
- \(C_s\) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
- \(C_0\) = nominal concentration of amlodipine in the Sample solution (mg/mL)
- \(M_1\) = molecular weight of amlodipine, 408.88
- \(M_2\) = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of the labeled amount of olmesartan medoxomil \((\text{C}_{25}\text{H}_{18}\text{N}_{4}\text{O}_3)\) in the portion of Tablets taken:

\[
\text{Result} = \left(\frac{r_0}{r_s}\right) \times \left(\frac{C_0}{C_s}\right) \times 100
\]

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PERFORMANCE TESTS

Change to read:

• DISSOLUTION (711)
  Test 1A (611.1-Mar-2020)
  Medium: 6.8 g/L of potassium phosphate, monobasic. Adjust with 0.2 N sodium hydroxide solution to a pH of 6.8; 900 mL.
  Apparatus 2: 50 rpm
  Times
  Amlodipine: 30 min
  Olmesartan medoxomil: 45 min
  Buffer: 4.08 g/L of potassium phosphate, monobasic. Adjust with phosphoric acid to a pH of 2.5.
  Mobile phase: Acetonitrile and Buffer (40:60)
  Standard solution A: 0.16 mg/mL of USP Amlodipine Besylate RS in Mobile phase
  Standard solution B: 0.44 mg/mL of USP Olmesartan Medoxomil RS in Mobile phase
  Standard solution: 0.016 mg/mL of USP Amlodipine Besylate RS and 0.044 mg/mL of USP Olmesartan Medoxomil RS in Medium from Standard solution A and Standard solution B
  Apparatus 2: Pass a portion of the solution under test through a suitable filter of 0.45-μm pore size and discard the first 2–3 mL of the filtrate.
  Chromatographic system
  (See Chromatography (621), System Suitability.)
  Mode: LC
  Detector: UV 254 nm
  Column: 4.6-mm x 15-cm; 5-μm packing L1
  Autosampler temperature: 5°
  Flow rate: 1.2 mL/min
  Injection volume: 10 μL
  Run time: NLT 1.4 times the retention time of amlodipine
  System suitability
  Sample: Standard solution
  Suitability requirements
  Tailing factor: NMT 2.0 for amlodipine and olmesartan medoxomil peaks
  Relative standard deviation: NMT 2.0% for amlodipine and olmesartan medoxomil peaks
  Analysis
  Samples: Standard solution and Sample solution
  Calculate the percentage of the labeled amount of amlodipine (C₂₉H₃₅ClN₃O₇) dissolved:
  \[
  \text{Result} = \left( \frac{r_1}{r_2} \right) \times C_t \times V \times (M_t/M_s) \times (1/L) \times 100
  \]
  \( r_1 \) = peak response of amlodipine from the Sample solution
  \( r_2 \) = peak response of amlodipine from the Standard solution
  \( C_t \) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
  \( V \) = volume of Medium, 900 mL
  \( M_t \) = molecular weight of amlodipine, 408.88
  \( M_s \) = molecular weight of Olmesartan Medoximol RS, 567.05
  \( L \) = label claim of amlodipine (mg/Tablet)
  Calculate the concentration (\( C_t \) or \( C_s \)) of olmesartan medoxomil (C₂₉H₃₉N₂O₇) in the sample withdrawn from the vessel at the 30- or 45-min time point:
  \[
  \text{Result} = \left( \frac{r_1}{r_2} \right) \times C_t
  \]
  \( r_1 \) = peak response of olmesartan medoxomil from the Sample solution at the 30- or 45-min time point
  \( r_2 \) = peak response of olmesartan medoxomil from the Standard solution
  \( C_t \) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)
  Calculate the percentage of the labeled amount of olmesartan medoxomil (C₂₉H₃₉N₂O₇) dissolved:
  \[
  \text{Result} = \left( \frac{C_x \times (V - V_2) + (C_t \times V_2)}{1/L} \right) \times 100
  \]
  \( C_x \) = concentration of Olmesartan medoxomil in the Sample solution at the 45-min time point (mg/mL)
  \( V \) = volume of Medium, 900 mL
  \( V_2 \) = volume of the Sample solution withdrawn at the 30- or 45-min time point (mL)
  \( C_t \) = concentration of Olmesartan medoxomil RS in the Sample solution at the 30- or 45-min time point (mg/mL)
  \( L \) = label claim of olmesartan medoxomil (mg/Tablet)
  Tolerances: NLT 80.0% (Q) of the labeled amount of amlodipine (C₂₉H₃₅ClN₃O₇) at 30 min and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil (C₂₉H₃₉N₂O₇) at 45 min are dissolved.
  Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
  Medium: 6.8 g/L of potassium phosphate monobasic and 0.9 g/L of sodium hydroxide. Adjust with 10% sodium hydroxide solution to a pH of 6.8; 900 mL.
  Apparatus 2: 50 rpm
  Times
  Amlodipine: 30 min
  Olmesartan medoxomil: 30 min
  Buffer: Add 2 mL of triethylamine in 1000 mL of water. Adjust with phosphoric acid to a pH of 2.5.
  Mobile phase: Acetonitrile and Buffer (30:70)
  Standard solution A: 0.15 mg/mL of USP Amlodipine Besylate RS in methanol
  Standard solution B: 0.44 mg/mL of USP Olmesartan Medoximol RS in methanol
  Standard solution: Known concentrations of USP Amlodipine Besylate RS and USP Olmesartan Medoximol RS in Medium from Standard solution A and Standard solution B, prepared per Table 4.

<table>
<thead>
<tr>
<th>Tablet Strength Amlodipine/ Olmesartan Medoxo- mil (mg/mg)</th>
<th>Concentration of USP Amlodipine Besylate RS (mg/mL)</th>
<th>Concentration of USP Olmesartan Me- doxomil RS (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20</td>
<td>0.0075</td>
<td>0.022</td>
</tr>
<tr>
<td>5/40</td>
<td>0.0075</td>
<td>0.044</td>
</tr>
<tr>
<td>10/20</td>
<td>0.015</td>
<td>0.022</td>
</tr>
</tbody>
</table>
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.

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

Mode: LC
Detector: UV 236 nm
Column: 4.6-mm × 5-cm; 5-µm packing
Temperatures
Autosampler: 5°
Column: 30°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
Run time: NLT 1.5 times the retention time of olmesartan medoxomil

System suitability
Sample: Standard solution
[Note—The relative retention times for olmesartan, amlodipine, and olmesartan medoxomil are 0.29, 0.68, and 1.00, respectively.]

Suitability requirements
Tailing factor: NMT 2.0 for amlodipine and olmesartan medoxomil peaks
Relative standard deviation: NMT 2.0% for amlodipine and olmesartan medoxomil peaks

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{3}) dissolved:

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

\[ r_U \] = peak response of amlodipine from the Sample solution
\[ r_s \] = peak response of amlodipine from the Standard solution
\[ C_s \] = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
\[ V \] = volume of Medium, 900 mL
\[ M_1 \] = molecular weight of amlodipine, 408.88
\[ M_2 \] = molecular weight of amlodipine besylate, 567.05
\[ L \] = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{4}O_{6}) dissolved:

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

\[ r_U \] = sum of peak responses of olmesartan and olmesartan medoxomil from the Sample solution
\[ r_s \] = sum of 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)

Tolerances: NLT 75.0% (Q) of the labeled amount of amlodipine (C_{20}H_{25}ClN_{2}O_{3}) and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil (C_{29}H_{30}N_{4}O_{6}) are dissolved. \( \text{(RB 1-Mar-2020)} \)

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

**Impurities**

Change to read:

- **Organic impurities**


**Standard stock solution A:** 28 µg/mL of USP Amlodipine Besylate RS and 80 µg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution

**Standard stock solution B:** 50 µg/mL of USP Amlodipine Related Compound A RS in Diluent

**Standard solution:** 1.4 µg/mL of USP Amlodipine Besylate RS, 2.5 µg/mL of USP Amlodipine Related Compound A RS, and 4 µg/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution

**Sample solution:** Use the Sample stock solution, prepared as directed in the Assay.

**System suitability**

Samples: Standard solution and Sensitivity solution
[Note—See Table 4 at (RB 1-Mar-2020) for relative retention times.]

Suitability requirements
Tailing factor: NMT 2.0 for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Standard solution
Relative standard deviation: NMT 5.0% for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Standard solution
Signal-to-noise ratio: NLT 10 for amlodipine related compound A, amlodipine, and olmesartan medoxomil peaks, Sensitivity solution

Analysis
Samples: Standard solution and Sample solution
Calculate the percentage of amlodipine related compound A free base in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( C_s / C_U \right) \times \left( \frac{M_1}{M_2} \right) \times 100 \]

\[ r_U \] = peak response of amlodipine related compound A from the Sample solution
\[ r_s \] = peak response of amlodipine related compound A from the Standard solution
\[ C_s \] = concentration of USP Amlodipine Related Compound A RS in the Standard solution (mg/mL)
\[ C_U \] = nominal concentration of amlodipine in the Sample solution (mg/mL)
\[ M_1 \] = molecular weight of amlodipine related compound A free base, 406.86
\[ M_2 \] = molecular weight of amlodipine related compound A, 522.93

Calculate the percentage of any unspecified amlodipine related impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_s}{r_U} \right) \times \left( C_s / C_U \right) \times \left( \frac{M_1}{M_2} \right) \times 100 \]
4 Amlodipine

\[ r_U = \text{peak response of any unspecified amlodipine related impurity from the Sample solution} \]

\[ r_S = \text{peak response of amlodipine from the Standard solution} \]

\[ C_S = \text{concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)} \]

\[ C_U = \text{nominal concentration of amlodipine in the Sample solution (mg/mL)} \]

\[ M_r = \text{molecular weight of amlodipine, 408.88} \]

\[ M_{r2} = \text{molecular weight of amlodipine besylate, 567.05} \]

Calculate the percentage of olmesartan or any unspecified olmesartan medoxomil related impurity in the portion of Tablets taken:

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times 100 \]

\[ r_U = \text{peak response of olmesartan or any unspecified olmesartan medoxomil related impurity from the Sample solution} \]

\[ r_S = \text{peak response of olmesartan medoxomil from the Standard solution} \]

\[ C_S = \text{concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)} \]

\[ C_U = \text{nominal concentration of olmesartan medoxomil in the Sample solution (mg/mL)} \]

Acceptance criteria: See Table ▲5▲ (RB 1-Mar-2020)

Table ▲5▲ (RB 1-Mar-2020) (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzenesulfonic acid(^a)</td>
<td>0.13</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan(^b)</td>
<td>0.25</td>
<td>2.0</td>
</tr>
<tr>
<td>Amlodipine related compound A(^c)</td>
<td>0.36</td>
<td>0.5</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.47</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A(^d)</td>
<td>1.13</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan olefinic impurity(^e)</td>
<td>1.50</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan N-alkyl impurity(^f)</td>
<td>2.03</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) This peak is due to the counterion and is not to be reported or included in the total impurities.

\(^b\) 1-\((2'-(1H-Tetrazol-5-y1)biphenyl-4-yl)methyl\)-4-(2-hydroxypropan-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.

\(^c\) 3-Ethyl 5-methyl \((2-(2-aminothoxyethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate)\).

\(^d\) 1-\((2'-(1H-Tetrazol-5-y1)biphenyl-4-yl)methyl\)-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(4\(H\))-one.

\(^e\) 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.

\(^f\) (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl \((2'-(2-trityl-2\(H\)-tetrazol-5-y1)biphenyl-4-yl)methyl\)-1\(H\)-imidazole-5-carboxylate.

\(^g\) The relative retention times for unspecified amlodipine related impurities are up to 1.0. The relative retention times for unspecified olmesartan medoxomil related impurities are after 1.0 and also at 0.45, 0.60, 0.76, 0.79, and 0.92.

\(^h\) Excluding olmesartan.

**ADDITIONAL REQUIREMENTS**

- **PACKAGING AND STORAGE:** Preserve in tight containers, and store at controlled room temperature.

**ADD the following:**

**USP REFERENCE STANDARDS** (11)

USP Amlodipine Besylate RS
USP Amlodipine Related Compound A RS
3-Ethyl 5-methyl \([2-(2-aminothoxyethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate]\) fumarate.

\[ C_{20}H_{23}ClN_2O_5 \cdot C_4H_4O_4 = 522.93 \]

USP Olmesartan Medoxomil RS

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