Amlodipine and Olmesartan Medoxomil Tablets

<table>
<thead>
<tr>
<th>Type of Posting</th>
<th>Notice of Intent to Revise</th>
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<tr>
<td>Posting Date</td>
<td>24–Apr–2020</td>
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<tr>
<td>Targeted Official Date</td>
<td>To Be Determined, Revision Bulletin</td>
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<tr>
<td>Expert Committee</td>
<td>Chemical Medicines Monographs 2</td>
</tr>
</tbody>
</table>

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 Amlodipine and Olmesartan Medoxomil Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add Dissolution Test 3 to the monograph. This revision also necessitates a change in the table numbering in the test for Organic Impurities.

- The analytical procedure in Dissolution Test 3 was validated using a Waters Xterra RP18 brand of L1 column. The typical retention times for amlodipine and olmesartan medoxomil are 2.8 min and 6.5 min, respectively.

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 Yanyin Yang, Associate Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-692-3623 or yanyin.yang@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.
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 (C_{21}H_{15}ClN_{2}O_{3}) and NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil (C_{32}H_{18}N_{2}O_{4}).

**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.

**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>

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.

**Table 2**

<table>
<thead>
<tr>
<th>Table Strength</th>
<th>Amlodipine</th>
<th>Olmesartan Medoxomil (mg/mL)</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>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5/40</td>
<td>0.25</td>
<td>2</td>
<td>1.6</td>
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</tr>
<tr>
<td>10/20</td>
<td>0.5</td>
<td>2</td>
<td>1.6</td>
<td></td>
</tr>
</tbody>
</table>

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

**Table 3**

<table>
<thead>
<tr>
<th>Table Strength</th>
<th>Amlodipine</th>
<th>Olmesartan Medoxomil (mg/mL)</th>
<th>Nominal Concentration of Amlodipine (mg/mL)</th>
<th>Nominal Concentration of Olmesartan Medoxomil (mg/mL)</th>
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</thead>
<tbody>
<tr>
<td>5/20, 10/40</td>
<td>0.04</td>
<td>0.16</td>
<td>0.16</td>
<td></td>
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<tr>
<td>5/40</td>
<td>0.02</td>
<td>0.16</td>
<td>0.16</td>
<td></td>
</tr>
<tr>
<td>10/20</td>
<td>0.04</td>
<td>0.08</td>
<td>0.08</td>
<td></td>
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</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 (C_{21}H_{15}ClN_{2}O_{3}) in the portion of Tablets taken:

\[
\text{Result} = \frac{r_0}{r_1} \times \frac{C_1}{C_0} \times \left( M_1/M_2 \right) \times 100
\]

- \( r_0 \) = peak response of amlodipine from the Sample solution
- \( r_1 \) = peak response of amlodipine from the Standard solution
- \( C_1 \) = 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 (C_{32}H_{18}N_{2}O_{4}) in the portion of Tablets taken:

\[
\text{Result} = \frac{r_0}{r_2} \times \frac{C_1}{C_0} \times 100
\]
2 Amlodipine

\( r_v \) = 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 (mg/mL)
\( C_v \) = nominal concentration of olmesartan medoxomil in the Sample solution (mg/mL)

Acceptance criteria
Amlodipine: 90.0%–110.0%
Olmesartan medoxomil: 90.0%–110.0%

PERFORMANCE TESTS

Change to read:

- **Dissolution** (711)
  Test 1
  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 stock solution A: 0.16 mg/mL of USP Amlodipine Besylate RS in Mobile phase
  Standard stock solution B: 0.44 mg/mL of USP Olmesartan Medoxomil RS in Mobile phase
  Standard stock solution: 0.016 mg/mL of USP Amlodipine Besylate RS and 0.044 mg/mL of USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B
  Sample solution: 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°C
  Flow rate: 1.2 mL/min
  Injection volume: 10 μL
  Run time: NLT 1.4 times the retention time of olmesartan medoxomil

  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 ([C₆H₂₈O₇N₂]₃) dissolved:
  Result = \((r_v/r_s) \times C_v \times V \times (M_v/M_s)) \times (1/L) \times 100

  \( V \) = volume of Medium, 900 mL
  \( M_v \) = molecular weight of amlodipine, 408.88
  \( M_s \) = molecular weight of amlodipine besylate, 567.05
  \( L \) = label claim of amlodipine (mg/Tablet)

  Calculate the concentration \( C_v \) or \( C_s \) of olmesartan medoxomil ([C₆H₂₈O₇N₂]₃) in the sample withdrawn from the vessel at the 30- or 45-min time point:
  \[ \text{Result} = \left( \frac{r_v}{r_s} \right) \times C_v \]

  \( r_v \) = peak response of olmesartan medoxomil from the Sample solution at the 30- or 45-min time point
  \( r_s \) = peak response of olmesartan medoxomil from the Standard solution
  \( C_s \) = concentration of USP Olmesartan Medoxomil RS in the Standard solution (mg/mL)

  Calculate the percentage of the labeled amount of olmesartan medoxomil ([C₆H₂₈O₇N₂]₃) dissolved:
  \[ \text{Result} = \left( \frac{C_v}{C_s} \right) \times (V - V_s) \times (1/L) \times 100 \]

  \( C_v \) = concentration of olmesartan medoxomil in the Sample solution at the 45-min time point (mg/mL)
  \( V \) = volume of Medium, 900 mL
  \( V_s \) = volume of the Sample solution withdrawn at the 30-min time point (mL)
  \( C_s \) = concentration of olmesartan medoxomil in the Sample solution at the 30-min time point (mg/mL)
  \( L \) = label claim of olmesartan medoxomil (mg/Tablet)

  Tolerances: NLT 80.0% (Q) of the labeled amount of amlodipine ([C₆H₂₈O₇N₂]₃) at 30 min and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil ([C₆H₂₈O₇N₂]₃) 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 stock solution A: 0.15 mg/mL of USP Amlodipine Besylate RS in methanol
  Standard stock solution B: 0.44 mg/mL of USP Olmesartan Medoxomil RS in methanol
  Standard solution: Known concentrations of USP Amlodipine Besylate RS and USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B, prepared per Table 4.

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

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Table 4 (continued)

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Concentration of USP Amlodipine Bysylate (mg/mL)</th>
<th>Concentration of USP Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10/40</td>
<td>0.015</td>
<td>0.044</td>
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</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 L1

Temperatures

Autosampler: 5°C
Column: 30°C
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_{18}ClN_{3}O_{3}) dissolved:

Result = (r_0/r_s) × C_s × V × (M_a/M_o) × (1/L) × 100

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 Bysylate RS in the Standard solution (mg/mL)
V = volume of Medium, 900 mL
M_a = molecular weight of amlodipine, 408.88
M_o = molecular weight of amlodipine byssylate, 567.05
L = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of olmesartan medoxomil (C_{23}H_{35}N_{2}O_{3}) dissolved:

Result = (r_0/r_s) × C_s × V × (1/L) × 100

r_0 = 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_{18}ClN_{3}O_{3}) and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil (C_{23}H_{35}N_{2}O_{3}) are dissolved.

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

Medium: 7.8 g/L of sodium phosphate monobasic dihydrate and 0.1 g/L of polyoxyethylene (20) sorbitan monolaurate in water. Adjust with 2 N 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 4.7 g of sodium phosphate monobasic dihydrate and 1 mL of triethylamine to 1000 mL of water. Adjust with phosphoric acid to a pH of 4.0.

Mobile phase: Acetonitrile and Buffer (40:60)
Diluent: Acetonitrile and water (80:20)

Standard stock solution A: 0.31 mg/mL of USP Amlodipine Bysylate RS in Diluent

Standard stock solution B: 0.9 mg/mL of USP Olmesartan Medoxomil RS in Diluent

Standard solution: Known concentrations of USP Amlodipine Bysylate RS and USP Olmesartan Medoxomil RS in Medium from Standard stock solution A and Standard stock solution B prepared per Table 5.

Table 5

<table>
<thead>
<tr>
<th>Tablet Strength</th>
<th>Concentration of USP Amlodipine Bysylate RS (mg/mL)</th>
<th>Concentration of USP Olmesartan Medoxomil (mg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5/20</td>
<td>0.00775</td>
<td>0.0225</td>
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<tr>
<td>5/40</td>
<td>0.00775</td>
<td>0.045</td>
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<tr>
<td>10/20</td>
<td>0.0155</td>
<td>0.0225</td>
</tr>
<tr>
<td>10/40</td>
<td>0.0155</td>
<td>0.045</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 237 nm
Column: 4.6-mm × 15-cm; 5-μm packing L1

Temperatures

Autosampler: 10°C
Column: 30°C
Flow rate: 1.0 mL/min
Injection volume: 20 μL
Run time: NLT 1.6 times the retention time of olmesartan medoxomil

System suitability
Sample: Standard solution
[Note—The relative retention times for amlodipine and olmesartan medoxomil are about 0.51 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_{18}ClN_{3}O_{3}) dissolved:
4 Amlodipine

Result = \( r_0 \times C_s \times V \times (M_M/M_p) \times (1/L) \times 100 \)

- \( r_0 \): peak response of amlodipine from the Sample solution
- \( r_s \): peak response of amlodipine from the Standard solution
- \( C_s \): concentration of USP Amlodipine Blysate RS in the Standard solution (mg/mL)
- \( V \): volume of Medium, 900 mL
- \( M_M \): molecular weight of amlodipine, 408.88
- \( M_p \): molecular weight of amlodipine Blysate, 567.05
- \( L \): label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of olmesartan medoxomil (C\textsubscript{22}H\textsubscript{21}Cl\textsubscript{14}N\textsubscript{8}O\textsubscript{5}) dissolved:

Result = \( r_0/r_s \times C_s \times V \times (1/L) \times 100 \)

- \( r_0 \): 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 (mg/mL)
- \( V \): volume of Medium, 900 mL
- \( L \): label claim of olmesartan medoxomil (mg/Tablet)

Tolerances: NLT 80.0% (Q) of the labeled amount of amlodipine (C\textsubscript{20}H\textsubscript{16}Cl\textsubscript{14}N\textsubscript{5}O\textsubscript{3}) and NLT 80.0% (Q) of the labeled amount of olmesartan medoxomil (C\textsubscript{22}H\textsubscript{21}Cl\textsubscript{14}N\textsubscript{8}O\textsubscript{5}) are dissolved.

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

**Impurities**

**Change to read:**

- **Organic Impurities**
  - Standard stock solution A: 28 \( \mu \)g/mL of USP Amlodipine Blysate RS and 80 \( \mu \)g/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution
  - Standard stock solution B: 50 \( \mu \)g/mL of USP Amlodipine Related Compound A RS in Diluent
  - Standard solution: 1.4 \( \mu \)g/mL of USP Amlodipine Blysate RS, 2.5 \( \mu \)g/mL of USP Amlodipine Related Compound A RS, and 4 \( \mu \)g/mL of USP Olmesartan Medoxomil RS in Diluent from Standard stock solution A and Standard stock solution B
  - Sensitivity solution: 0.28 \( \mu \)g/mL of USP Amlodipine Blysate RS, 0.5 \( \mu \)g/mL of USP Amlodipine Related Compound A RS, and 0.8 \( \mu \)g/mL of USP Olmesartan Medoxomil RS in Diluent from Standard 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 *6* 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:

Result = \( r_0 / r_s \times (C_s / C_o) \times (M_M / M_p) \times 100 \)

- \( r_0 \): peak response of amlodipine related compound A from the Sample solution
- \( r_s \): peak response of amlodipine from the Standard solution
- \( C_s \): concentration of USP Amlodipine Related Compound A RS in the Standard solution (mg/mL)
- \( C_o \): nominal concentration of amlodipine in the Sample solution (mg/mL)
- \( M_M \): molecular weight of amlodipine related compound A free base, 406.86
- \( M_p \): molecular weight of amlodipine related compound A, 522.93

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

Result = \( r_0 / r_s \times (C_s / C_o) \times (M_M / M_p) \times 100 \)

- \( r_0 \): peak response of any unspecified amlodipine related impurity from the Sample solution
- \( r_s \): peak response of amlodipine from the Standard solution
- \( C_s \): concentration of USP Amlodipine Blysate RS in the Standard solution (mg/mL)
- \( C_o \): nominal concentration of amlodipine in the Sample solution (mg/mL)
- \( M_M \): molecular weight of amlodipine, 408.88
- \( M_p \): molecular weight of amlodipine Blysate, 567.05

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

Result = \( r_0 / r_s \times (C_s / C_o) \times 100 \)

- \( r_0 \): peak response of olmesartan or any unspecified olmesartan medoxomil related impurity 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 (mg/mL)
- \( C_o \): nominal concentration of olmesartan medoxomil in the Sample solution (mg/mL)

**Acceptance criteria:** See Table *6* for relative retention times.

### Table *6*:

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzylsulfonic acid(\d)</td>
<td>0.13</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan(\d)</td>
<td>0.25</td>
<td>2.0</td>
</tr>
<tr>
<td>Amlodipine related compound A(\d)</td>
<td>0.36</td>
<td>0.5</td>
</tr>
<tr>
<td>Amlodipine</td>
<td>0.47</td>
<td>—</td>
</tr>
</tbody>
</table>

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### Table 6A (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olmesartan medoxomil</td>
<td>1.0</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan medoxomil related compound A*</td>
<td>1.13</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan olefinic impurity*</td>
<td>1.50</td>
<td>—</td>
</tr>
<tr>
<td>Olmesartan N-alkyl impurity*</td>
<td>2.03</td>
<td>—</td>
</tr>
</tbody>
</table>
| Any unspecified amldipine or olmesartan medoxom related impurity  
  h                                                | —                      | 0.2                          |
| Total impurities                               | —                       | 2.0                          |

* This peak is due to the counterion and is not to be reported or included in the total impurities.

1. (Z)-(1H-Tetrazol-5-y)naphtyl-4-methyl-4-(2-hydroxyprop-2-yl)-2-propyl-1H-imidazole-5-carboxylic acid.
2. 3-Ethyl 5-methyl [2-(2-aminooxothymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
3. (Z)-(1H-Tetrazol-5-y)naphtyl-4-methyl-4,4-dimethyl-2-propyl-1H-furo[3,4-d]imidazol-6(1H)-one.

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.

5. (S-Methyl-2-oxo-1,3-dioxol-4-y)methyl 1-((2-(1H-tetrazol-5-y)naphtyl-4-y)methyl)-4(prop-1-en-2-y)-2-propyl-1H-imidazole-5-carboxylate.
6. (S-Methyl-2-oxo-1,3-dioxol-4-y)methyl 4-(2-hydroxyprop-2-yl)-2-propyl-1-((2-(2-tributy1-2H-tetrazol-5-y)naphtyl-4-y)methyl)-1H-imidazole-5-carboxylate.
7. The relative retention times for unspecified amldipine related impurities are up to 1.0. The relative retention times for unspecified olmesartan medoxomil related impurities are after 1.0 and also at 0.43, 0.60, 0.76, 0.79, and 0.92.
8. Excluding olmesartan.

### 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 Dissolution test used only if Test 1 is not used.
- **USP REFERENCE STANDARDS (11)**
  - USP Amlodipine Besylate RS
  - USP Amlodipine Related Compound A RS
  - 3-Ethyl 5-methyl [2-(2-aminooxothymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate] fumarate.
  - C₂₀H₂₃ClN₂O₅ • C₂H₅O₂ • 522.93
  - USP Olmesartan Medoxomil RS

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