Amlodipine and Olmesartan Medoxomil Tablets

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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 ($C_{20}H_{25}ClN_2O_5$) and NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$).

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

Time (min)	Solution A (%)	Solution B (%)
0	68	32
12	68	32
15	30	70
21	30	70
23	68	32
25	68	32

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

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Olmesartan Medoxomil (mg/mL)
5/20, 10/40	0.5	2
5/40	0.25	2
10/20	0.5	1

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

Table 3

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Amlodipine/ Olmesartan Medoxomil (mg/mL)
5/20, 10/40	0.04	0.16
5/40	0.02	0.16
10/20	0.04	0.08

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 ($C_{20}H_{25}ClN_2O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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)
C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

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* (mg/mL)
C_U = 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**▲ (RB 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 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 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 × 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 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 ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
L = label claim of amlodipine (mg/Tablet)

Calculate the concentration (C_1 or C_2) of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) in the sample withdrawn from the vessel at the 30- or 45-min time point:

$$\text{Result} = (r_U/r_S) \times C_S$$

r_U = 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 ($C_{29}H_{30}N_6O_6$) dissolved:

$$\text{Result} = \{[C_2 \times (V - V_S)] + (C_1 \times V_S)\} \times (1/L) \times 100$$

C_2 = 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_1 = 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 ($C_{20}H_{25}ClN_2O_5$) at 30 min and NLT 70.0% (*Q*) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) 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 4

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Concentration of USP Amlodipine Besylate RS (mg/mL)	Concentration of USP Olmesartan Medoxomil RS (mg/mL)
5/20	0.0075	0.022
5/40	0.0075	0.044
10/20	0.015	0.022

Table 4 *(continued)*

Tablet Strength Amlodipine/ Olmesartan Medoxomil (mg/mg)	Concentration of USP Amlodipine Besylate RS (mg/mL)	Concentration of USP Olmesartan Medoxomil RS (mg/mL)
10/40	0.015	0.044

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°
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 ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L) \times 100$$

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_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
L = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times 100$$

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 ($C_{20}H_{25}ClN_2O_5$) and NLT 70.0% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) are dissolved. ▲ (RB 1-Mar-2020)

• **UNIFORMITY OF DOSAGE UNITS** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **ORGANIC IMPURITIES**
Solution A, Solution B, Mobile phase, Diluent, Standard stock solution, Sample stock solution, and **Chromatographic system:** Proceed as directed in the *Assay*.
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 A* and *Standard stock solution B*
Sensitivity solution: 0.28 µg/mL of USP Amlodipine Besylate RS, 0.5 µg/mL of USP Amlodipine Related Compound A RS, and 0.8 µg/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* ▲5 ▲ (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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

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_{r1} = molecular weight of amlodipine related compound A free base, 406.86
M_{r2} = molecular weight of amlodipine related compound A, 522.93

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

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = 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 Besylate RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = 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:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times 100$$

r_U = 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_U = 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)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzenesulfonic acid[a]	0.13	—
Olmesartan[b]	0.25	2.0
Amlodipine related compound A[c]	0.36	0.5
Amlodipine	0.47	—
Olmesartan medoxomil	1.0	—
Olmesartan medoxomil related compound A[d, e]	1.13	—
Olmesartan olefinic impurity[f, e]	1.50	—
Olmesartan *N*-alkyl impurity[g, e]	2.03	—
Any unspecified amlodipine or olmesartan medoxomil related impurity[h]	—	0.2
Total impurities[i]	—	2.0

[a] This peak is due to the counterion and is not to be reported or included in the total impurities.
[b] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carboxylic acid.
[c] 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
[d] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4,4-dimethyl-2-propyl-1*H*-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 1-((2′-(1*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-4-(prop-1-en-2-yl)-2-propyl-1*H*-imidazole-5-carboxylate.
[g] (5-Methyl-2-oxo-1,3-dioxol-4-yl)methyl 4-(2-hydroxypropan-2-yl)-2-propyl-1-((2′-(2-trityl-2*H*-tetrazol-5-yl)biphenyl-4-yl)methyl)-1*H*-imidazole-5-carboxylate.
[h] 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.
[i] Excluding olmesartan.

ADDITIONAL REQUIREMENTS

- **Packaging and Storage:** Preserve in tight containers, and store at controlled room temperature.

Add the following:

▲• **Labeling:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.▲ (RB 1-Mar-2020)

- **USP Reference Standards** ⟨11⟩
  USP Amlodipine Besylate RS
  USP Amlodipine Related Compound A RS
  3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-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