Olmesartan Medoxomil Tablets

Type of Posting	Revision Bulletin
Posting Date	31–Jan–2020
Official Date	01–Feb–2020
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 add *Dissolution Test 7* to accommodate FDA-approved drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

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

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

Olmesartan Medoxomil Tablets

DEFINITION

Olmesartan Medoxomil Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$).

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 1

Time (min)	Solution B (%)	Solution C (%)
0	68.8	31.2
1.5	37.5	62.5
1.6	68.8	31.2
3.0	68.8	31.2

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°
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 ($C_{29}H_{30}N_6O_6$) 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* (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 ($C_{29}H_{30}N_6O_6$) dissolved:

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

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

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

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*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) 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

Time (min)	Solution A (%)	Solution B (%)
0	75	25
4.0	52	48
5.0	75	25
7.0	75	25

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°
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_1) of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) in the *Sample solution*:

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

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)

Calculate the concentration (C_2) of olmesartan as olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) in the *Sample solution*:

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

r_U = peak response of olmesartan 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)
F = relative response factor, 0.88
M_{r2} = molecular weight of olmesartan medoxomil, 558.59
M_{r1} = molecular weight of olmesartan, 446.50

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

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

C_1 = 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 ($C_{29}H_{30}N_6O_6$) is dissolved.
Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.
Medium: 0.1 M hydrochloric acid; 900 mL

Apparatus 2: 50 rpm
Time: 15 min
Buffer: Dissolve 2.04 g of monobasic potassium phosphate in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (40:60)
Diluent: Acetonitrile and water (60:40)
Standard stock solution: 1.1 mg/mL of USP Olmesartan Medoxomil RS in *Diluent*
Standard solution
[NOTE—Preserve immediately 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*
[NOTE—The relative retention times for olmesartan and olmesartan medoxomil are 0.24 and 1.00, respectively.]
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 ($C_{29}H_{30}N_6O_6$) dissolved:

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

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)

Tolerances: NLT 80% (*Q*) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) is dissolved.
Test 6: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 6*.
Medium: 0.05 M pH 6.8 phosphate buffer (dissolve 68 g of monobasic potassium phosphate and 9 g of sodium hydroxide in 10,000 mL of water; adjust with diluted sodium hydroxide solution or diluted phosphoric acid to a pH of 6.8); 900 mL
Apparatus 2: 50 rpm
Time: 30 min
Buffer: Dissolve 6.8 g of monobasic potassium phosphate in 1000 mL of water. Adjust with diluted phosphoric acid to a pH of 3.0.
Mobile phase: Acetonitrile and *Buffer* (40:60)
Diluent: Acetonitrile and water (50:50)
Standard stock solution A: 0.55 mg/mL of USP Olmesartan Medoxomil RS in *Diluent*. Sonication may be needed to dissolve.
For Tablets labeled to contain 5 mg
Standard stock solution B: 5.5 µg/mL of USP Olmesartan Medoxomil RS in *Medium* from *Standard stock solution A*
Standard solution: 2.75 µg/mL of USP Olmesartan Medoxomil RS in *Mobile phase* from *Standard stock solution B*
For Tablets labeled to contain 20 mg
Standard stock solution C: 22 µg/mL of USP Olmesartan Medoxomil RS in *Medium* from *Standard stock solution A*
Standard solution: 11 µg/mL of USP Olmesartan Medoxomil RS in *Mobile phase* from *Standard stock solution C*
For Tablets labeled to contain 40 mg
Standard stock solution D: 44 µg/mL of USP Olmesartan Medoxomil RS in *Medium* from *Standard stock solution A*
Standard solution: 22 µg/mL of USP Olmesartan Medoxomil RS in *Mobile phase* from the *Standard stock solution D*
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Transfer 5.0 mL of the filtrate into a 10-mL volumetric flask. Dilute with *Mobile phase* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size. [NOTE—The *Sample solution* is stable for 25 h at 5°.]
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Autosampler: 5°
Column: 30°
Flow rate: 2.0 mL/min
Injection volume: 100 µL
Run time: NLT 1.5 times the retention time of olmesartan medoxomil
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) dissolved:

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

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)
D = dilution factor for the *Sample solution*
V = volume of *Medium*, 900 mL

L = label claim of olmesartan medoxomil (mg/Tablet)

Tolerances: NLT 70% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) is dissolved.

▲**Test 7:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 7*.
Medium: 0.1 N hydrochloric acid; 900 mL
Apparatus 2: 50 rpm
Time: 20 min
Diluent: Acetonitrile and water (60:40)
Standard stock solution: 1.12 mg/mL of USP Olmesartan Medoxomil RS in *Diluent*
Standard solution
For Tablets labeled to contain 5 mg: 5.6 µg/mL of USP Olmesartan Medoxomil RS in *Medium* from the *Standard stock solution*
For Tablets labeled to contain 20 mg or 40 mg: 11.2 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 at least the first 5 mL of the filtrate. Dilute with *Medium* to a concentration that is similar to the *Standard solution* if necessary.
Instrumental conditions
(See *Ultraviolet-Visible Spectroscopy* ⟨857⟩.)
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 ($C_{29}H_{30}N_6O_6$) dissolved:

$$\text{Result} = (A_U/A_S) \times C_S \times D \times V \times (1/L) \times 100$$

A_U = absorbance of the *Sample solution*
A_S = absorbance of the *Standard solution*
C_S = concentration of USP Olmesartan Medoxomil RS in the *Standard solution* (mg/mL)
D = dilution factor of the *Sample solution*
V = volume of *Medium*, 900 mL
L = label claim (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of olmesartan medoxomil ($C_{29}H_{30}N_6O_6$) is dissolved. ▲ (RB 1-Feb-2020)

• **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*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0	75	25
10	75	25
35	0	100
45	0	100

Diluent: Acetonitrile and water (90:10)
System suitability solution: 0.01 mg/mL each of USP Olmesartan Medoxomil RS and USP Olmesartan Medoxomil Related Compound A RS in *Diluent*
Standard 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 × 10-cm; 3.5-µm packing L7
Column temperature: 40°
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:

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

r_U = peak response of each degradation product 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)
F = relative response factor (see *Table 4*)

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

Table 4

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Olmesartan[a]	0.2	1.0	2.5
Olmesartan medoxomil related compound A[b]	0.7	1.6	—
Olmesartan medoxomil	1.0	—	—
Olmesartan dimer[c]	1.2	0.8	0.5
Olefinic impurity[d]	1.5	1.0	0.6
Any unspecified degradation product	—	1.0	0.2

Table 4 *(continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Total degradation products	—	—	4.1

[a] 1-{[2′-(1*H*-Tetrazol-5-yl)biphenyl-4-yl]methyl}-4-(2-hydroxypropan-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-{[1-({2′-(1*H*-tetrazol-5-yl)-[1,1′-biphenyl]-4-yl}methyl)-4-(2-hydroxypropan-2-yl)-2-propyl-1*H*-imidazole-5-carbonyl]oxy}propan-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}-4,4-dimethyl-2-propyl-1*H*-furo[3,4-*d*]imidazol-6(4*H*)-one.
  $C_{24}H_{24}N_6O_2$ 428.49