Olmesartan Medoxomil Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	25–Jan–2019
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Expert Committee	Chemical Medicines Monographs 2

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 Olmesartan Medoxomil Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 4* to the monograph.

- *Dissolution Test 4* was validated using the Kromasil C18 brand of L1 column. The typical retention times for olmesartan and olmesartan medoxomil are about 0.8 and 3.5 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 Donald Min, Senior Scientific Liaison to the Chemical Medicines Monographs 2 Expert Committee (301-230-7457 or ddm@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*.

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.▲ (TBD)

• **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 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
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