Olmesartan Medoxomil Tablets

Type of Posting	Revision Bulletin
Posting Date	30–Aug–2019
Official Date	01–Sep–2019
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* 6 to accommodate drug products with different dissolution conditions and/or tolerances than the existing dissolution tests.

- *Dissolution Test 6* was validated using the Thermo Scientific Hypersil BDS C18 brand of column with L1 packing. The typical retention time for olmesartan medoxomil is between 2.5 and 3.5 min.

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

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Donald Min, Senior Scientific Liaison (301-230-7457 or ddm@usp.org).

[1] Note: Addition of *Dissolution Test 5* to the Olmesartan Medoxomil Tablets monograph is currently being proposed under the Pending Monograph process.

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. ▲ (RB 1-Sep-2019)

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

IMPURITIES

Change to read:

- **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▲ (ERR 1-Sep-2019) 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