Olmesartan Medoxomil Tablets

Type of Posting	Revision Bulletin
Posting Date	28–July–2017
Official Date	01–Aug–2017
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. The purpose for the revision is to add *Dissolution Test 2* to accommodate the FDA approved drug products with different dissolution conditions and tolerance than the existing dissolution test. A *Labeling* section is also added. Because there is no 10-mg tablet product in the US market, *Sample stock solution* section in the *Assay* is revised to remove 10-mg tablet strength.

The Olmesartan Medoxomil Tablets Revision Bulletin supersedes the monograph that was scheduled to become official in the *First Supplement* to *USP 40–NF 35*. The Revision Bulletin will be incorporated in the *First Supplement* to *USP 41–NF 36*.

Should you have any questions, please contact Edith Chang, Scientific Liaison (301-816-8392 or yec@usp.org).

Add the following:

▪Olmesartan Medoxomil Tablets

DEFINITION
Olmesartan Medoxomil Tablets contain NLT 93.0% and NMT 105.0% 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

Change to read:

- **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- ● (RB 1-Aug-2017) 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 B*, 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: 93.0%–105.0%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

●Test 1● (RB 1-Aug-2017)
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.• (RB 1-Aug-2017)

• **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 2*.

Table 2

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 3*)

Acceptance criteria: See *Table 3*. Disregard peaks below 0.1%.

Table 3

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

[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.

Table 3 *(Continued)*

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
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.

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-Aug-2017)
- **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

■1S (*USP40*)