

Olmesartan Medoxomil Tablets

Type of Posting	Revision Bulletin
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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 widen the acceptance criteria for the *Definition* and *Assay* of olmesartan medoxomil from NLT 93.0% and NMT 105.0% to NLT 90.0% and NMT 110.0% based on the manufacturers' FDA-approved drug product specifications and to add *Dissolution Test 3* to accommodate FDA-approved drug products with different tolerances than the existing dissolution tests.

- *Dissolution Test 3* was validated using a Zorbax Rx C8 brand of L7 column. The typical retention time for olmesartan medoxomil is about 3.8 min.

The revision also necessitates a change in the table numbering in the *Organic Impurities* test.

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

Should you have any questions, please contact Donald Min, Senior Scientific Liaison (301-230-7457 or ddm@usp.org) or Tsion Bililign, Scientific Liaison (301-816-8286 or tb@usp.org).

Olmесartan Medoxomil Tablets

Change to read:

DEFINITION

Olmесartan Medoxomil Tablets contain NLT $\blacktriangle 90.0\%$ \blacktriangle (RB 1-Nov-2018) and NMT $\blacktriangle 110.0\%$ \blacktriangle (RB 1-Nov-2018) 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 μ g/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 μ g/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 \times 5-cm; 1.7- μ m packing L1
Column temperature: 35°
Flow rate: 0.6 mL/min
Injection volume: 1 μ L
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* (μ g/mL)
 C_U = nominal concentration of olmesartan medoxomil in the *Sample solution* (μ g/mL)

Acceptance criteria: $\blacktriangle 90.0\%$ – 110.0% \blacktriangle (RB 1-Nov-2018)

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- μ m 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- μ m 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 μ g/mL of USP Olmesartan Medoxomil RS in *Diluent B* from the *Standard stock solution*

For Tablets labeled to contain 20 mg: 11 μ g/mL of USP Olmesartan Medoxomil RS in *Diluent B* from the *Standard stock solution*

For Tablets labeled to contain 40 mg: 22 μ g/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- μ m 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 \times 15-cm; 5- μ m packing L7

Temperatures

Autosampler: 5°

Column: 30°

Flow rate: 1.5 mL/min

Injection volume: 10 μ L

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.▲ (RB 1-Nov-2018)

- **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▲ (RB 1-Nov-2018)

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- μ m pore size.

Chromatographic system

(See *Chromatography* <621>, *System Suitability*.)

Mode: LC

Detector: UV 250 nm

Column: 4.6-mm \times 10-cm; 3.5- μ m packing L7

Column temperature: 40°

Flow rate: 1 mL/min

Injection volume: 10 μ L

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)▲ (RB 1-Nov-2018)

Acceptance criteria: See ▲Table 4.▲ (RB 1-Nov-2018) Disregard peaks below 0.1%.

▲Table 4▲ (RB 1-Nov-2018)

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