Telmisartan and Amlodipine Tablets

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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 Telmisartan and Amlodipine Tablets monograph. The purpose for the revision is to add *Dissolution Test 2* to accommodate FDA-approved drug products with different dissolution conditions and tolerances than the existing dissolution test.

- *Dissolution Test 2* lists separate HPLC methods for telmisartan and amlodipine, which are validated using a Symmetry C8 brand of L7 column. The typical retention times for telmisartan and amlodipine are about 2.5 and 3.1 min, respectively.

- *Labeling* information has been incorporated to support the inclusion of *Dissolution Test 2*.

The Telmisartan and Amlodipine 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).

Telmisartan and Amlodipine Tablets

DEFINITION

Telmisartan and Amlodipine Tablets contain NLT 90.0% and NMT 110.0% of the labeled amount each of telmisartan ($C_{33}H_{30}N_4O_2$) and amlodipine ($C_{20}H_{25}ClN_2O_5$).

IDENTIFICATION

- **A.** The retention times of the two major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.
- **B.** The UV spectra of the two major peaks of the *Sample solution* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Buffer: 0.022 M monobasic sodium phosphate dihydrate and 2 mL of triethylamine in 1 L of water. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (40:60)

Diluent: Add 5 mL of triethylamine to 500 mL of water. Add 500 mL of acetonitrile and mix.

Standard stock solution 1: 0.4 mg/mL of USP Telmisartan RS in *Diluent*

Standard stock solution 2: 0.4 mg/mL of USP Amlodipine Besylate RS in *Diluent*

Standard solution: 0.08 mg/mL of USP Telmisartan RS and 0.03 mg/mL of USP Amlodipine Besylate RS in *Diluent* from *Standard stock solution 1* and *Standard stock solution 2*

Sample stock solution: Nominally 0.4 mg/mL of telmisartan and 0.1 mg/mL of amlodipine from Tablets prepared as follows. Transfer NLT 10 Tablets to a suitable volumetric flask. Add acetonitrile to about 20% of the volume of the flask, and sonicate for 5 min with intermittent shaking. Add *Diluent* to about 80% of the volume of the flask and sonicate until the Tablets are completely dispersed. Dilute with *Diluent* to the volume. Centrifuge and use the supernatant.

Sample solution: Nominally 0.08 mg/mL of telmisartan and 0.02 mg/mL of amlodipine from *Sample stock solution* in *Diluent*. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 257 nm. For *Identification B*, use a diode array detector in the range of 200–350 nm.

Column: 4.6-mm × 25-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: 20 min

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for amlodipine and telmisartan are 0.5 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 2.0 for telmisartan; NMT 2.5 for amlodipine

Relative standard deviation: NMT 2.0% for telmisartan and amlodipine

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) in the portion of Tablets taken:

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

r_U = peak response of telmisartan from the *Sample solution*

r_S = peak response of telmisartan from the *Standard solution*

C_S = concentration of USP Telmisartan RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of telmisartan in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of amlodipine from the *Sample solution*

r_S = peak response of amlodipine from the *Standard solution*

C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution* (mg/mL)

C_U = nominal concentration of amlodipine besylate in the *Sample solution* (mg/mL)

M_{r1} = molecular weight of amlodipine, 408.88

M_{r2} = molecular weight of amlodipine besylate, 567.05

Acceptance criteria: 90.0%–110.0% each of telmisartan and amlodipine

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (RB 1-Nov-2018)

Test for telmisartan

Medium: pH 7.5 phosphate buffer (0.05 M monobasic potassium phosphate and 0.038 M sodium hydroxide in 1 L of water; adjusted with diluted sodium hydroxide solution to a pH of 7.5); 900 mL

Apparatus 2: 75 rpm

Time: 20 min

Buffer: 0.022 M monobasic sodium phosphate dihydrate and 2 mL of triethylamine in 1 L of water. Adjust with phosphoric acid to a pH of 6.0.

Mobile phase: Acetonitrile and *Buffer* (40:60)

Diluent: Add 5 mL of triethylamine to 500 mL of water. Add 500 mL of acetonitrile and mix.

Standard stock solution: 0.9 mg/mL of USP Telmisartan RS in *Diluent*. [NOTE—Sonication may be required to aid dissolution.]

Standard solution: 0.045 mg/mL of USP Telmisartan RS from *Standard stock solution* in *Medium*

Sample solution: Pass a portion of the solution under test through a suitable filter with suitable pore size.

Chromatographic system

(See *Chromatography* ⟨621⟩, *System Suitability*.)

Mode: LC

Detector: UV 257 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 1 mL/min

Injection volume: 20 µL

Run time: 12 min

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 telmisartan ($C_{33}H_{30}N_4O_2$) dissolved:

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

r_U = peak response of telmisartan from the *Sample solution*
r_S = peak response of telmisartan from the *Standard solution*
C_S = concentration of USP Telmisartan RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*, if needed
V = volume of *Medium*, 900 mL
L = label claim of telmisartan (mg/Tablet)

Test for amlodipine
Medium: 0.01 N hydrochloric acid; 500 mL
Apparatus 2: 75 rpm
Time: 20 min
Mobile phase and **Chromatographic system:** Proceed as directed in *Dissolution*, *Test for telmisartan*.
Standard stock solution: 0.7 mg/mL of USP Amlodipine Besylate RS in *Medium*. [NOTE—Sonication may be required to aid dissolution.]
Standard solution: 0.03 mg/mL of USP Amlodipine Besylate RS from *Standard stock solution* in *Medium*
Sample solution: Pass a portion of the solution under test through a suitable filter of suitable pore size.
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.5
Relative standard deviation: NMT 2.0%
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times (C_S \times D) \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of amlodipine from the *Sample solution*
r_S = peak response of amlodipine from the *Standard solution*
C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution* (mg/mL)
D = dilution factor for the *Sample solution*, if needed
V = volume of *Medium*, 500 mL
L = label claim of amlodipine (mg/Tablet)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Tolerances: NLT 80% (Q) of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) is dissolved. NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Test for telmisartan
Medium: pH 7.5 phosphate buffer (6.805 g/L of monobasic potassium phosphate and 1.6 g/L of sodium hydroxide in water; adjusted with 5 N sodium hydroxide solution or phosphoric acid to a pH of 7.5); 900 mL
Apparatus 2: 75 rpm
Time: 30 min
Buffer: 1.54 g/L of ammonium acetate in water. Adjust with acetic acid to a pH of 5.0.
Mobile phase: Acetonitrile and *Buffer* (50:50)
Diluent: 0.01 N hydrochloric acid
Standard stock solution: 0.56 mg/mL of USP Telmisartan RS, prepared as follows. Transfer a quantity of USP Telmisartan RS to a suitable volumetric flask. Add 40% of the total volume of both methanol and *Diluent*. Sonicate to dissolve. Dilute with *Diluent* to volume and mix well.
Standard solution
For Tablets labeled to contain 80 mg of telmisartan: 0.09 mg/mL of USP Telmisartan RS in *Medium* from the *Standard stock solution*
For Tablets labeled to contain 40 mg of telmisartan: 0.045 mg/mL of USP Telmisartan 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.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Temperatures
Autosampler: 10°
Column: 35°
Flow rate: 1.5 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of the telmisartan peak
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*
[NOTE—The relative retention times for amlodipine and telmisartan are 0.69 and 1.00, respectively.]
Calculate the percentage of the labeled amount of telmisartan ($C_{33}H_{30}N_4O_2$) dissolved:

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

r_U = peak response of telmisartan from the *Sample solution*
r_S = peak response of telmisartan from the *Standard solution*
C_S = concentration of USP Telmisartan RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L = label claim of telmisartan (mg/Tablet)

Test for amlodipine
Medium: 0.01 N hydrochloric acid; 500 mL
Apparatus 2: 75 rpm
Time: 30 min

Buffer: 1.54 g/L of ammonium acetate in water. Adjust with acetic acid to a pH of 5.0.
Mobile phase: Acetonitrile and *Buffer* (40:60)
Standard stock solution: 0.35 mg/mL of USP Amlodipine Besylate RS prepared as follows. Transfer a quantity of USP Amlodipine Besylate RS to a suitable volumetric flask. Add 5% of the total volume of methanol. Sonicate to dissolve. Dilute with water to volume and mix well.
Standard solution
For Tablets labeled to contain 10 mg of amlodipine: 0.028 mg/mL of USP Amlodipine Besylate RS in *Medium* from the *Standard stock solution*
For Tablets labeled to contain 5 mg of amlodipine: 0.014 mg/mL of USP Amlodipine Besylate 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.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 238 nm
Column: 4.6-mm × 15-cm; 5-µm packing L7
Temperatures
Autosampler: 10°
Column: 35°
Flow rate: 1.5 mL/min
Injection volume: 40 µL
Run time: NLT 2.5 times the retention time of the amlodipine peak
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*
[NOTE—The relative retention times for amlodipine and telmisartan are 1.0 and 1.9, respectively.]
Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of amlodipine from the *Sample solution*
r_S = peak response of amlodipine from the *Standard solution*
C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 500 mL
L = label claim of amlodipine (mg/Tablet)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Tolerances: NLT 80% (Q) of the labeled amount each of telmisartan ($C_{33}H_{30}N_4O_2$) and amlodipine ($C_{20}H_{25}ClN_2O_5$) are dissolved.▲ (RB 1-Nov-2018)

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

IMPURITIES

- **ORGANIC IMPURITIES**

Buffer 1: 0.023 M ammonium acetate in water. Adjust with phosphoric acid to a pH of 5.5.
Solution A: Acetonitrile and *Buffer 1* (20:80)
Solution B: Acetonitrile and *Buffer 1* (65:35)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
5	95	5
15	70	30
35	45	55
50	5	95
65	0	100
70	0	100
75	95	5
80	95	5

Buffer 2: 0.023 M ammonium acetate in water. Adjust with phosphoric acid to a pH of 2.0.
Diluent: Acetonitrile and *Buffer 2* (40:60)
Standard stock solution 1: 0.5 mg/mL of USP Telmisartan RS in *Diluent*
Standard stock solution 2: 0.17 mg/mL of USP Amlodipine Besylate RS in *Diluent*
Standard solution: 25 µg/mL of USP Telmisartan RS from *Standard stock solution 1* and 4.25 µg/mL of USP Amlodipine Besylate RS from *Standard stock solution 2* in *Diluent*
Sensitivity solution: 0.25 µg/mL of USP Telmisartan RS from *Standard stock solution 1* and 0.11 µg/mL of USP Amlodipine Besylate RS from *Standard stock solution 2* in *Diluent*
Sample solution: Nominally 0.25 mg/mL of amlodipine prepared as follows. Transfer a suitable quantity, nominally equivalent to 25 mg of amlodipine from finely powdered Tablets (NLT 10), to a suitable volumetric flask. Add *Diluent* to 70% of the volume of the flask. Sonicate in cold water for 15 min with intermittent shaking. Dilute with *Diluent* to volume. Pass a portion of the solution through a suitable filter of 0.45-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 257 nm
Column: 4.6-mm × 25-cm; 5-µm packing L1
Temperatures
Autosampler: 10°
Column: 30°
Flow rate: 1 mL/min
Injection volume: 20 µL
System suitability
Samples: *Standard solution* and *Sensitivity solution*
[NOTE—The relative retention times for amlodipine and telmisartan are 0.74 and 1.0, respectively.]
Suitability requirements
Tailing factor: NMT 2.5, *Standard solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Signal-to-noise ratio: NLT 10, *Sensitivity solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of amlodipine related compound D or amlodipine mannitol adduct in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (1/F) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of amlodipine related compound D or amlodipine mannitol adduct from the *Sample solution*
r_S = peak response of amlodipine from the *Standard solution*
C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (µg/mL)
F = relative response factor (see *Table 2*)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of each individual unspecified degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times (M_{r1}/M_{r2}) \times 100$$

r_U = peak response of each individual unspecified degradation product from the *Sample solution*
r_S = peak response of amlodipine from the *Standard solution*
C_S = concentration of USP Amlodipine Besylate RS in the *Standard solution* (µg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (µg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Acceptance criteria: See *Table 2*. Disregard any peak less than 0.1%.

Table 2

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Besylate[a]	0.08	—	—
Amlodipine related compound D[b]	0.59	0.39	1.0
Amlodipine mannitol adduct	0.67	1.00	0.50
Amlodipine	0.74	—	—
Telmisartan related compound A[c, d]	0.78	—	—
Telmisartan related compound B[d, e]	0.86	—	—
Telmisartan	1.0	—	—
Any individual unspecified degradation product	—	—	0.2
Total degradation products	—	—	2.0

[a] Peak due to besylate (benzenesulfonic acid).
[b] 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-{[2-(1,3-dioxoisoindolin-2-yl)ethoxy] methyl}-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
[c] 1,7′-Dimethyl-2′-propyl-1*H*,3′*H*-2,5′-bibenzo[*d*]imidazole.
[d] Process impurities controlled in the drug substance.
[e] 4′-[(1,7′-Dimethyl-2′-propyl-1*H*,1′*H*-2,5′-bibenzo[*d*]imidazol-1′-yl)methyl] biphenyl-2-carboxylic acid.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in tight 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-Nov-2018)

- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Amlodipine Besylate RS
  USP Telmisartan RS