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 (C11H10N4O5) and amlodipine (C20H25ClN2O6).

**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 (C11H10N4O5) and the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_0}{r_1} \right) \times \left( \frac{C_f}{C_i} \right) \times 100
\]

where:
- \(r_0\) = peak response of telmisartan from the Sample solution
- \(r_1\) = peak response of telmisartan from the Standard solution
- \(C_i\) = concentration of USP Telmisartan RS in the Standard solution (mg/mL)
- \(C_f\) = nominal concentration of telmisartan in the Sample solution (mg/mL)

Calculate the percentage of the labeled amount of amlodipine (C20H25ClN2O6) in the portion of Tablets taken:

\[
\text{Result} = \left( \frac{r_0}{r_2} \right) \times \left( \frac{C_f}{C_i} \right) \times \left( \frac{M_f}{M_i} \right) \times 100
\]

where:
- \(r_0\) = peak response of amlodipine from the Sample solution
- \(r_2\) = peak response of amlodipine from the Standard solution
- \(C_i\) = concentration of USP Amlodipine Besylate RS in the Standard solution (mg/mL)
- \(C_f\) = nominal concentration of amlodipine besylate in the Sample solution (mg/mL)
- \(M_{f1}\) = molecular weight of amlodipine, 408.88
- \(M_{f2}\) = molecular weight of amlodipine besylate, 567.05

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

**PERFORMANCE TESTS**

* Dissolution (711)
* Test 1 (881-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 from Standard stock solution
Standard solution: 0.045 mg/mL of USP Telmisartan from Standard stock solution
Sample solution: 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 0.04 mg/mL of telmisartan and 0.02 mg/mL of amlodipine from Sample 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
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
Telmisartan

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 \( (C_{21}H_{29}N_3O_2) \) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_1} \right) \times \left( C_s \times D \right) \times V \times (1/L) \times 100
\]

\( r_0 \) = peak response of telmisartan from the Sample solution

\( r_1 \) = 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 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 3 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 suitable pore size.

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 \( (C_{21}H_{29}N_3O_2) \) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_1} \right) \times \left( C_s \times D \right) \times V \times (1/L) \times 100
\]

\( r_0 \) = peak response of telmisartan from the Sample solution

\( r_1 \) = 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: 30 min

Analysis

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

Calculate the percentage of the labeled amount of telmisartan \( (C_{31}H_{29}ClN_2O_2) \) dissolved:

\[
\text{Result} = \left( \frac{r_0}{r_1} \right) \times C_s \times V \times (1/L) \times 100
\]

\( r_0 \) = peak response of telmisartan from the Sample solution

\( r_1 \) = peak response of telmisartan from the Standard solution

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

\( V \) = volume of Medium, 900 mL

\( L \) = label claim of telmisartan (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of telmisartan \( (C_{21}H_{29}N_3O_2) \) is dissolved. NLT 80% (Q) of the labeled amount of telmisartan \( (C_{31}H_{29}ClN_2O_2) \) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that it meets USP Dissolution Test 2.
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 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 2.5
Relative standard deviation: NMT 2.0%

Analysis
Samples: Standard solution and Sample solution

Result = \( \left( \frac{r_1}{r_2} \right) \times C \times V \times (1/L) \times (M_{10}/M_{12}) \times 100 \)

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

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

Result = \( \left( \frac{r_1}{r_2} \right) \times C \times V \times (1/L) \times (M_{10}/M_{12}) \times 100 \)

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**Telmisartan 3**

NOTE—The relative retention times for amlodipine and telmisartan are 1.0 and 1.9, respectively.

The relative standard deviations for amlodipine and telmisartan are 0.74 and 1.0, respectively.

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:

Result = \( \left( \frac{r_1}{r_2} \right) \times C \times V \times (1/L) \times (M_{10}/M_{12}) \times 100 \)
4 Telmisartan

\[ r_U = \text{peak response of amlodipine related compound D or amlodipine mannitol adduct from the Sample solution} \]

\[ r_S = \text{peak response of amlodipine from the Standard solution} \]

\[ C_S = \text{concentration of USP Amlodipine Besylate RS in the Standard solution} (\mu g/mL) \]

\[ C_U = \text{nominal concentration of amlodipine in the Sample solution} (\mu g/mL) \]

\[ F = \text{relative response factor (see Table 2)} \]

\[ M_{r1} = \text{molecular weight of amlodipine, 408.88} \]

\[ M_{r2} = \text{molecular weight of amlodipine besylate, 567.05} \]

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

\[ \text{Result} = \left( \frac{r_U}{r_S} \right) \times \left( \frac{C_S}{C_U} \right) \times \left( \frac{M_{r1}}{M_{r2}} \right) \times 100 \]

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

### Table 2 (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Relative Retention Time</th>
<th>Relative Response Factor</th>
<th>Acceptance Criteria, NMT (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Besylate(^a)</td>
<td>0.08</td>
<td>—</td>
<td>—</td>
</tr>
</tbody>
</table>

\(^a\) Peak due to besylate (benzenesulfonic acid).

\(^b\) 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[(2-(1,3-dioxaioindolin-2-yl)ethoxy)methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

\(^c\) 1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenz[d]imidazole.

\(^d\) Process impurities controlled in the drug substance.

\(^e\) 4′-[(1,7′-Dimethyl-2′-propyl-1H,3′H-2,5′-bibenz[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:**

\(^\Delta\) **LABELING:** When more than one Dissolution test is given, the labeling states the Dissolution test used only if Test 1 is not used.\(^\Delta\) (RB 1-Nov-2018)

• **USP REFERENCE STANDARDS** (11)
  - USP Amlodipine Besylate RS
  - USP Telmisartan RS