Amlodipine and Valsartan 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 Amlodipine and Valsartan Tablets monograph. The purpose of this revision is to be consistent with the FDA-approved drug products and is described below:

- The acceptance criteria under *Definition* and *Assay* is widened from “NLT 95.0% and NMT 105.0%” to “NLT 90.0% and NMT 110.0%” for both amlodipine and valsartan.
- The acceptance criterion for total degradation products is widened from NMT 0.8% to NMT 1.2%.
- A *Dissolution Test 2* is added. The liquid chromatographic procedure is validated using an Inertsil ODS 3V brand of L1 column. The typical retention times for amlodipine and valsartan are about 4.3 min and 7.0 min respectively.
- A *Dissolution Test 3* is added. The liquid chromatographic procedure is validated using an Oyster ODS 3 brand of L1 column. The typical retention times for amlodipine and valsartan are about 3.0 min and 3.5 min respectively.

Minor editorial changes have been made to update the monograph to the current *USP* style.

The Amlodipine and Valsartan Tablets Revision Bulletin supersede the currently official Amlodipine and Valsartan Tablets monograph. The Revision Bulletin will be incorporated in the *USP 40–NF 35.*

Should you have any questions, please contact Sujatha Ramakrishna, Ph.D., MBA. Senior Scientific Liaison (301–816–8349 or sxr@usp.org)

Amlodipine and Valsartan Tablets

DEFINITION

Change to read:

Amlodipine and Valsartan Tablets contain •NLT 90.0% and NMT 110.0%• (RB 1-Jun-2016) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and valsartan ($C_{24}H_{29}N_5O_3$).

IDENTIFICATION

- **A.** The UV absorption spectra of the major peaks of *Sample solution A* and *Sample solution B* and those of the *Standard solution* exhibit maxima and minima at the same wavelengths, as obtained in the *Assay*.
- **B.** The retention times of the major peaks of *Sample solution A* and *Sample solution B* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

Change to read:

- **PROCEDURE**

Solution A: Water and triethylamine (1000:10). Adjust with phosphoric acid to a pH of 2.8.
Solution B: Methanol and acetonitrile (700:300)
Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	50	50
3	50	50
15	30	70
20	30	70
20.1	50	50
25	50	50

Diluent: *Solution A* and *Solution B* (50:50)
Standard solution: 0.14 mg/mL of USP Amlodipine Besylate RS and 0.16 mg/mL of USP Valsartan RS. Add methanol to 5% of the final volume to dissolve, and dilute with *Diluent* to volume.
Sample stock solution: Transfer NLT 10 Tablets into a suitable volumetric flask. Initially add water to 10% of the final volume, and sonicate to disperse as needed. Add *Diluent*, using about 70% of the final volume, and shake for up to 45 min to disperse. Following dispersion, sonicate for 15 min, and shake for 30 min. Dilute with *Diluent* to volume to obtain a solution containing known nominal concentrations of 0.1–0.2 mg/mL of amlodipine and 1.6–6.4 mg/mL of valsartan. Centrifuge the solution for about 10 min at 3000 rpm.
Sample solution A: Nominally equivalent to 0.1 mg/mL of amlodipine in *Diluent* from *Sample stock solution*
Sample solution B: Nominally equivalent to 0.16 mg/mL of valsartan in *Diluent* from *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector
Assay: UV 237 nm
Identification A: Diode array, •UV 200–400 nm• (RB 1-Jun-2016)
Column: 3.9-mm × 15-cm; 5-µm packing L1
Temperatures
Autosampler: 10°
Column: 30°
Flow rate: 1.0 mL/min
Injection volume: 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 1.5 for both amlodipine and valsartan
Relative standard deviation: NMT 2.0% for amlodipine and valsartan
Analysis
Samples: *Standard solution*, *Sample solution A*, and *Sample solution B*
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 *Sample solution A*
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 in *Sample solution A* (mg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) in the portion of Tablets taken:

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

r_U = peak response of valsartan from *Sample solution B*
r_S = peak response of valsartan from the *Standard solution*
C_S = concentration of USP Valsartan RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valsartan in *Sample solution B* (mg/mL)

Acceptance criteria: •90.0%–110.0%• (RB 1-Jun-2016)

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

•**Test 1**• (RB 1-Jun-2016)
Buffer: Dissolve 6.805 g of monobasic potassium phosphate and 0.896 g of sodium hydroxide in water, and dilute with water to 1000 mL. Adjust with 0.2 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8.
Medium: *Buffer*; 1000 mL
Apparatus 2: 75 rpm
Time: 30 min
Mobile phase: Acetonitrile, water, and trifluoroacetic acid (500:500:2)
Diluent: 1 mg/mL of polysorbate 80 in *Buffer*
System suitability solution: 0.4 mg/mL each of USP Amlodipine Besylate RS and USP Valsartan RS prepared as follows. Initially dissolve in methanol to 40% of the total volume, and dilute with *Buffer* to volume.
Standard stock solution A: 0.072 mg/mL of USP Amlodipine Besylate RS prepared as follows. Initially

dissolve in methanol to 4% of the final volume, and dilute with *Diluent* to volume.
Standard stock solution B: 2.2 mg/mL of USP Valsartan RS in methanol
Standard solution: (L_1/1000) mg/mL of amlodipine and (L_2/1000) mg/mL of valsartan in *Diluent* from *Standard stock solution A* and *Standard stock solution B*, where L_1 is the label claim of amlodipine in mg/Tablet, and L_2 is the label claim of valsartan in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard the first 10 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 230 nm
Column: 4.6-mm × 15-cm; 4-µm packing L11
Column temperature: 40°
Flow rate: 1.2 mL/min
Injection volume: 10 µL
Run time: NLT 2 times the retention time of amlodipine
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 2.0 between amlodipine and valsartan, *System suitability solution*
Tailing factor: NMT 2.0 for amlodipine and valsartan, *Standard solution*
Relative standard deviation: NMT 2.0% for amlodipine and valsartan, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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*, 1000 mL
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
L_1 = label claim for amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

r_U = peak response of valsartan from the *Sample solution*
r_S = peak response of valsartan from the *Standard solution*
C_S = concentration of USP Valsartan RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 1000 mL
L_2 = label claim for valsartan (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and valsartan ($C_{24}H_{29}N_5O_3$) is dissolved.
•**Test 2:** If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
Medium and **Time:** Proceed as directed in *Dissolution Test 1*; 1000 mL.
Apparatus 2: 50 rpm
Buffer: Mix 7.0 mL of triethyamine with 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.
Solution A: Acetonitrile and *Buffer* (10:90)
Solution B: Acetonitrile and *Buffer* (90:10)
Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	80	20
7	30	70
8	80	20
10	80	20

Standard stock solution A: 0.14 mg/mL of USP Amlodipine Besylate RS prepared as follows. Initially dissolve in 10% of the final volume of methanol, and dilute with *Medium* to volume.
Standard stock solution B: 1.6 mg/mL of USP Valsartan RS in methanol
Standard solution: (L_1/1000) mg/mL of amlodipine and (L_2/1000) mg/mL of valsartan in *Diluent* from *Standard stock solution A* and *Standard stock solution B*, where L_1 is the label claim of amlodipine in mg/Tablet, and L_2 is the label claim of valsartan in mg/Tablet.
Sample solution: Pass a portion of the solution under test through a suitable filter of 1-µm pore size.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 237 nm
Column: 4.6-mm × 15-cm; 5-µm packing L1
Temperatures
Autosampler: 10°
Column: 50°
Flow rate: 1.5 mL/min
Injection volume: 20 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for amlodipine and valsartan
Relative standard deviation: NMT 2.0% for amlodipine and valsartan
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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*, 1000 mL
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
L_1 = label claim for amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

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

r_S = peak response of valsartan from the *Standard solution*
C_S = concentration of USP Valsartan RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 1000 mL
L_2 = label claim for valsartan (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and NLT 80% (*Q*) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved.

Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.

Medium, Apparatus 2, and **Time:** Proceed as directed in *Dissolution Test 1*.

Solution A: Acetonitrile, trifluoroacetic acid, and water (10: 0.1: 90)

Solution B: Acetonitrile, trifluoroacetic acid, and water (90: 0.1: 10)

Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0.01	90	10
2.5	10	90
3.0	90	10
5.0	90	10

Diluent: Acetonitrile and water (50:50)

Standard stock solution A: 0.14 mg/mL of USP Amlodipine Besylate RS prepared as follows. Initially dissolve in *Diluent* about 4% of the final volume, and dilute with *Medium* to volume.

Standard stock solution B: 1.6 mg/mL of USP Valsartan RS prepared as follows. Initially dissolve in about 20% of the final volume of *Diluent*, and dilute with *Medium* to volume.

Standard solution: (L_1/1000) mg/mL of amlodipine and (L_2/1000) mg/mL of valsartan in *Medium* from *Standard stock solution A* and *Standard stock solution B*, where L_1 is the label claim of amlodipine in mg/Tablet, and L_2 is the label claim of valsartan 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 mL of the filtrate.

Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 237 nm for amlodipine and UV 270 nm for valsartan
Column: 4.6-mm × 10-cm; 5-µm packing L1
Flow rate: 1.5 mL/min
Injection volume: 10 µL

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for amlodipine and valsartan
Relative standard deviation: NMT 2.0% for amlodipine and valsartan

Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (M_{r1}/M_{r2}) \times (1/L_1) \times 100$$

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*, 1000 mL
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
L_1 = label claim for amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_2) \times 100$$

r_U = peak response of valsartan from the *Sample solution*
r_S = peak response of valsartan from the *Standard solution*
C_S = concentration of USP Valsartan RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 1000 mL
L_2 = label claim for valsartan (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and NLT 80% (*Q*) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved.

● (RB 1-Jun-2016)

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

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES**

Mobile phase, Diluent, Sample solution A, Sample solution B, and **Chromatographic system:** Proceed as directed in the *Assay*.

Standard stock solution A: Prepare as directed for the *Standard solution* in the *Assay*.

System suitability solution: Dissolve a suitable quantity of USP Valsartan Related Compound B RS in *Standard stock solution A* to obtain a solution containing 0.08 mg/mL of USP Valsartan Related Compound B RS, 0.14 mg/mL of USP Amlodipine Besylate RS, and 0.16 mg/mL of USP Valsartan RS.

Sensitivity solution: 0.14 µg/mL of USP Amlodipine Besylate RS and 0.16 µg/mL of USP Valsartan RS in *Diluent* from *Standard stock solution A*

Standard stock solution B: 0.1 mg/mL of USP Amlodipine Related Compound A RS as free base prepared as follows. Add methanol to 5% of the final volume to dissolve, and dilute with *Diluent* to volume.

Standard solution: 0.0005 mg/mL of USP Amlodipine Related Compound A RS as free base, and 0.0003 mg/mL each of USP Amlodipine Besylate RS and USP Valsartan RS in *Diluent* from *Standard stock solution A* and *Standard stock solution B*, respectively

System suitability
Samples: *System suitability solution*, *Sensitivity solution*, and *Standard solution*
Suitability requirements
Resolution: More than 4.0 between amlodipine and valsartan related compound B and more than 4.0 between valsartan related compound B and valsartan, *System suitability solution*
Relative standard deviation: NMT 5.0% for amlodipine related compound A, amlodipine, and valsartan, *Standard solution*
Signal-to-noise ratio: NLT 10 for amlodipine and valsartan, *Sensitivity solution*

Analysis

Samples: *Sample solution A*, *Sample solution B*, and *Standard solution*

Calculate the percentage of amlodipine related compound A free base 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 related compound A from *Sample solution A*
r_S = peak response of amlodipine related compound A from the *Standard solution*
C_S = concentration of USP Amlodipine Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of amlodipine in *Sample solution A* (mg/mL)
M_{r1} = molecular weight of amlodipine related compound A free base, 406.86
M_{r2} = molecular weight of amlodipine related compound A fumarate, 522.93

Calculate the percentage of valsartan related degradation product in the portion of Tablets taken:

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

r_U = peak response of valsartan related degradation product from *Sample solution B*
r_S = peak response of valsartan from the *Standard solution*
C_S = concentration of USP Valsartan RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valsartan in *Sample solution B* (mg/mL)

Calculate the percentage of each 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 unspecified degradation product from *Sample solution A*
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 in *Sample solution A* (mg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

Acceptance criteria: See *Table 4*. Disregard valsartan related compound B, the benzenesulfonic acid peak at relative retention time 0.19, and any peaks below 0.1%.

Table 4

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Devaleryl valsartan[a]	0.24	0.2
Amlodipine related compound A[b]	0.50	0.5
Valsartan related degradation product 1[c]	0.54	0.2
Valsartan related degradation product 2[c]	0.81	0.2
Amlodipine	1.00	—
Valsartan related compound B[d]	1.34	—
Valsartan related degradation product 3[c]	1.44	0.2
Valsartan	1.74	—
Valsartan related degradation product 4[c]	2.06	0.2
Valsartan ethyl ester[e]	2.32	0.2
Any other unspecified degradation product	—	0.2
Total degradation products	—	●1.2● (RB 1-Jun-2016)

[a] *N*-{[2′-(1*H*-Tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.
[b] 3-Ethyl, 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
[c] These are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities.
[d] *N*-Butyryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.
[e] *N*-Valeryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine ethyl ester.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store at controlled room temperature, in tight containers, and in a dry place.

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-Jun-2016)
- **USP REFERENCE STANDARDS** ⟨11⟩
  USP Amlodipine Besylate RS
  USP Amlodipine Related Compound A RS
  3-Ethyl, 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate] fumarate.
  $C_{20}H_{23}ClN_2O_5 \cdot C_4H_4O_4$ 522.93
  USP Valsartan RS
  USP Valsartan Related Compound B RS
  N-Butyryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.
  $C_{23}H_{27}N_5O_3$ 421.49