Amlodipine and Valsartan Tablets

DEFINITION

Amlodipine and Valsartan Tablets contain NLT 90.0% and NMT 110.0% 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

- **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 the *Sample stock solution*
Sample solution B: Nominally equivalent to 0.16 mg/mL of valsartan in *Diluent* from the *Sample stock solution*
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 237 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.
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%

PERFORMANCE TESTS

Change to read:

- **DISSOLUTION** ⟨711⟩

Test 1
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 of 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 of 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 triethylamine 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 ●*Medium*● (IRA 1-Nov-2017) 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 of 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 of valsartan (mg/Tablet)

Tolerances: NLT 75% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved 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 milliliters 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 of 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 of valsartan (mg/Tablet)

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

- **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 •products other than valsartan related compound A• (IRA 1-Nov-2017) 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•[f]• (IRA 1-Nov-2017)	—	1.2; •2.0, if valsartan related compound A is a potential degradation product• (IRA 1-Nov-2017)

[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.
•[f] If valsartan related compound A is a potential degradation product, the total degradation products limit does not include valsartan related compound A and amlodipine related compound A.• (IRA 1-Nov-2017)

Add the following:

••LIMIT OF VALSARTAN RELATED COMPOUND A

[NOTE—Valsartan related compound A is a process impurity and a formulation-specific degradation product.]

Mobile phase: *n*-Hexane, 2-propanol, and trifluoroacetic acid (850:150:1)

System suitability solution: 0.04 mg/mL each of USP Valsartan Related Compound A and USP Valsartan RS in *Mobile phase*

Standard solution: 0.001 mg/mL of USP Valsartan Related Compound A RS in *Mobile phase*

Sample solution: Nominally 0.5 mg/mL of valsartan in *Mobile phase* from a suitable amount of finely crushed powder from NLT 20 Tablets. Sonication may be necessary for complete dissolution. Pass 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 × 25-cm; 5-µm packing L40

Temperatures

Autosampler: 10°

Column: 30°

Flow rate: 0.8 mL/min

Injection volume: 20 µL

Run time: NLT 3.5 times the retention time of valsartan related compound A

System suitability
Samples: *System suitability solution* and *Standard solution*
[NOTE—The relative retention times for valsartan related compound A and valsartan are about 0.7 and 1.0, respectively.]
Suitability requirements
Resolution: NLT 2.0 between valsartan and valsartan related compound A, *System suitability solution*
Relative standard deviation: NMT 5.0% for valsartan related compound A, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of valsartan related compound A 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 compound A from the *Sample solution*
r_S = peak response of valsartan related compound A from the *Standard solution*
C_S = concentration of USP Valsartan Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of valsartan in the *Sample solution* (mg/mL)
Acceptance criteria: NMT 1.0 %● (IRA 1-Nov-2017)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store at controlled room temperature, in tight containers, and in a dry place.
- **LABELING:** When more than one *Dissolution* test is given, the labeling states the *Dissolution* test used only if *Test 1* is not used.

Change to read:

- **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 A RS
N-Valeryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]methyl}-D-valine.
$C_{24}H_{29}N_5O_3$ 435.52● (IRA 1-Nov-2017)
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