Amlodipine, Valsartan, and Hydrochlorothiazide Tablets

DEFINITION

Amlodipine, Valsartan, and Hydrochlorothiazide Tablets contain NLT 92.5% and NMT 107.5% each of the labeled amounts of amlodipine ($C_{20}H_{25}ClN_2O_5$), valsartan ($C_{24}H_{29}N_5O_3$), and hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$).

IDENTIFICATION

- **A.** The UV absorption spectra of the amlodipine, valsartan, and hydrochlorothiazide peaks of *Sample solution A*, *Sample solution B*, and *Sample solution C*, 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 amlodipine, valsartan, and hydrochlorothiazide peaks of *Sample solution A*, *Sample solution B*, and *Sample solution C* correspond to those of the *Standard solution*, as obtained in the *Assay*.

ASSAY

- **PROCEDURE**

Use amber glassware for all solutions containing drug substances.

Solution A: Acetonitrile, water, and phosphoric acid (50:950:1)

Solution B: Acetonitrile, water, and phosphoric acid (950:50:1)

Mobile phase: See *Table 1*.

Table 1

Time (min)	Solution A (%)	Solution B (%)
0	95	5
3	50	50
6	40	60
10	5	95
10.1	95	5
15	95	5

Diluent: Acetonitrile and water (500:500)

0.1% Phosphoric acid: Water and phosphoric acid (1000:1)

Standard solution: 0.14 mg/mL of USP Amlodipine Besylate RS, 0.064 mg/mL of USP Valsartan RS, and 0.025 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

Sample stock solution: Transfer NLT 10 Tablets into a suitable volumetric flask. Add *0.1% Phosphoric acid* to 4% of the total volume to disperse the Tablets. Sonicate for 10 min. Add 4% of the total volume of acetonitrile, swirl to mix, and add 60% of the total volume of *Diluent*. Sonicate for 20 min. Dilute with *Diluent* to volume to obtain solutions of nominal concentrations stated in *Table 2*. Centrifuge, and use the clear supernatant.

Table 2

Tablet Strength Amlodipine/ Valsartan/ Hydrochlorothiazide (mg/mg/mg)	Nominal Concentration of Amlodipine (mg/mL)	Nominal Concentration of Valsartan (mg/mL)	Nominal Concentration of Hydrochlorothiazide (mg/mL)
5/160/12.5	0.1	3.2	0.25
10/160/12.5	0.2	3.2	0.25
5/160/25	0.1	3.2	0.5
10/160/25	0.2	3.2	0.5
10/320/25	0.1	3.2	0.25

Sample solution A: Nominally equivalent to 0.1 mg/mL of amlodipine in *Diluent* from *Sample stock solution*

Sample solution B: Nominally equivalent to 0.064 mg/mL of valsartan in *Diluent* from *Sample stock solution*

Sample solution C: Nominally equivalent to 0.025 mg/mL of hydrochlorothiazide in *Diluent* from *Sample stock solution*

Chromatographic system

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

Mode: LC

Detector: UV 225 nm. For *Identification A*, use a diode array detector in the range of 200–400 nm.

Column: 4.6-mm × 15-cm; 3-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection volume: 10 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide

Relative standard deviation: NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide

Analysis

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

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)

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) in the portion of Tablets taken:

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

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

Acceptance criteria: 92.5%–107.5%

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 1000 mL of water. Adjust with 0.2 N sodium hydroxide or 1 M phosphoric acid to a pH of 6.8.
Medium: *Buffer*; 900 mL
Apparatus 2
For 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 50 rpm
For 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 55 rpm
Time: 30 min
Solution A: Acetonitrile, water, and phosphoric acid (50:950:1)
Solution B: Acetonitrile, water, and phosphoric acid (950:50:1)
Mobile phase: See *Table 3*.

Table 3

Time (min)	Solution A (%)	Solution B (%)
0.00	67	33
2.50	23	77
2.51	67	33
4.00	67	33

Diluent: 1 mg/mL of polysorbate 80 in *Buffer*
Standard stock solution A: 0.07 mg/mL of USP Amlodipine Besylate and 0.124 mg/mL of USP Hydrochlorothiazide RS. Initially dissolve with 4% of the total volume of methanol, and dilute with *Diluent* to volume.
Standard stock solution B: 3.2 mg/mL of USP Valsartan RS in methanol
Standard solution: 0.014 mg/mL of USP Amlodipine Besylate RS, 0.16 mg/mL of USP Valsartan RS, and 0.0248 mg/mL of USP Hydrochlorothiazide RS in *Diluent* from *Standard stock solution A* and *Standard stock solution B*, respectively
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard at least the first 10 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 250 nm
Column: 4.6-mm × 5-cm; 3-µm packing L1
Column temperature: 30°
Flow rate: 1.5 mL/min
Injection volume
For 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 5 µL
For 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide): 10 µL
System suitability
Sample: *Standard solution*
Suitability requirements
Resolution: NLT 3.0 between amlodipine and valsartan
Tailing factor: NMT 2.0 for amlodipine, valsartan, and hydrochlorothiazide
Relative standard deviation: NMT 2.0% for amlodipine, valsartan, and hydrochlorothiazide
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*, 900 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*, 900 mL
L_2 = label claim of valsartan (mg/Tablet)

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_3) \times 100$$

r_U = peak response of hydrochlorothiazide from the *Sample solution*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L_3 = label claim of hydrochlorothiazide (mg/Tablet)

Tolerances: NLT 75% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved, NLT 80% (Q) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved, and NLT 80% (Q) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

Test 2: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 2*.
Medium: Proceed as directed under *Dissolution Test 1*; 900 mL.
Apparatus 2
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 5/80/12.5 (mg/mg/mg): 50 rpm
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg): 55 rpm
Times
For valsartan and hydrochlorothiazide: 30 min
For amlodipine: 45 min
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 4*.

Table 4

Time (min)	Solution A (%)	Solution B (%)
0	90	10
7	30	70
8	90	10
15	90	10

Standard stock solution A: 0.35 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 stock solution C: 0.7 mg/mL of USP Hydrochlorothiazide RS, prepared as follows. Initially dissolve in 25% of the final volume of methanol and dilute with *Medium* to volume.
Standard solution: (L_1/1000) mg/mL of amlodipine, (L_2/1000) mg/mL of valsartan, and (L_3/1000) mg/mL of hydrochlorothiazide in •*Medium*• (IRA 1-Nov-2017) from *Standard stock solution A*, *Standard stock solution B*, and *Standard stock solution C*, where L_1 is the label claim of amlodipine in mg/Tablet, L_2 is the label claim of valsartan in mg/Tablet, and L_3 is the label claim of hydrochlorothiazide 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 each peak
Relative standard deviation: NMT 2.0% for each peak
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*, 900 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*, 900 mL
L_2 = label claim of valsartan (mg/Tablet)
Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_3) \times 100$$

r_U = peak response of hydrochlorothiazide from the *Sample solution*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
L_3 = label claim of hydrochlorothiazide (mg/Tablet)
Tolerances: NLT 75% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved, NLT 80% (*Q*) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved, and NLT 80% (*Q*) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.
Test 3: If the product complies with this test, the labeling indicates that the product meets USP *Dissolution Test 3*.
Medium: Dissolve 6.80 g of monobasic potassium phosphate in 1000 mL of water. Adjust with 10% sodium hydroxide solution to a pH of 6.8; 1000 mL for valsartan and hydrochlorothiazide; 900 mL for amlodipine.
Apparatus 2
For valsartan and hydrochlorothiazide: 50 rpm
For amlodipine in Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg): 55 rpm
For amlodipine in Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, 10/160/25, and 5/80/12.5 (mg/mg/mg): 50 rpm
Times
For valsartan and hydrochlorothiazide: 30 min
For amlodipine: 45 min
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 5*.

Table 5

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: 0.15 mg/mL of USP Amlodipine Besylate RS in *Medium*, prepared as follows. Initially dissolve and sonicate in 5% of the final volume of *Diluent*, and dilute with *Medium* to volume.
Standard stock solution B: 1.6 mg/mL of USP Valsartan RS in *Medium*, prepared as follows. Initially dissolve and sonicate in 20% of the final volume of *Diluent*, and dilute with *Medium* to volume.
Standard stock solution C: 0.25 mg/mL of USP Hydrochlorothiazide RS in *Medium*, prepared as follows. Initially dissolve and sonicate in 10% of the final volume of *Diluent*, and dilute with *Medium* to volume.
Standard solution: (L_1/1000) mg/mL of amlodipine, (L_2/1000) mg/mL of valsartan, and (L_3/1000) mg/mL of hydrochlorothiazide in *Diluent* from *Standard stock solution A*, *Standard stock solution B*, and *Standard stock solution C*, where L_1 is the label claim of amlodipine in mg/Tablet, L_2 is the label claim of valsartan in mg/Tablet, and L_3 is the label claim of hydrochlorothiazide in mg/Tablet
Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size. Discard at least the first few milliliters of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detectors
For amlodipine: UV 237 nm
For valsartan and hydrochlorothiazide: UV 270 nm
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 each peak
Relative standard deviation: NMT 2.0% for each peak
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*, 900 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)

Calculate the percentage of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) dissolved:

$$\text{Result} = (r_U/r_S) \times C_S \times V \times (1/L_3) \times 100$$

r_U = peak response of hydrochlorothiazide from the *Sample solution*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 1000 mL
L_3 = label claim of hydrochlorothiazide (mg/Tablet)

Tolerances
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/12.5, 10/160/12.5, 5/160/25, and 10/160/25 (mg/mg/mg): NLT 75% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved, NLT 80% (*Q*) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved, and NLT 80% (*Q*) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.
For Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 5/160/25, and 10/320/25 (mg/mg/mg): NLT 70% (*Q*) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) is dissolved, NLT 80% (*Q*) of the labeled amount of valsartan ($C_{24}H_{29}N_5O_3$) is dissolved, and NLT 80% (*Q*) of the labeled amount of hydrochlorothiazide ($C_7H_8ClN_3O_4S_2$) is dissolved.

• **Uniformity of Dosage Units** ⟨905⟩**:** Meet the requirements

IMPURITIES

Change to read:

• **Organic Impurities**
Use amber glassware for all solutions containing drug substances.
Mobile phase, Diluent, Sample solution A, Sample solution B, Sample solution C, and **Chromatographic system:** Proceed as directed in the *Assay*.
System suitability solution: 0.02 mg/mL each of USP Benzothiadiazine Related Compound A RS and USP Valsartan Related Compound B RS, 0.005 mg/mL of USP Amlodipine Related Compound A RS, 0.14 mg/mL of USP Amlodipine Besylate RS, 0.064 mg/mL of USP Valsartan RS, and 0.025 mg/mL of USP Hydrochlorothiazide RS in *Diluent*
Sensitivity solution: 0.14 µg/mL of USP Amlodipine Besylate RS, 0.064 µg/mL of USP Valsartan RS, and 0.025 µg/mL of USP Hydrochlorothiazide RS in *Diluent*
Standard solution: 0.0005 mg/mL of USP Amlodipine Related Compound A RS, 0.0001 mg/mL of USP Benzothiadiazine Related Compound A RS, 0.0003 mg/mL of USP Amlodipine Besylate RS, 0.00015 mg/mL of

USP Valsartan RS, and 0.00005 mg/mL of USP Hydrochlorothiazide RS in *Diluent*

System suitability

Samples: *System suitability solution*, *Sensitivity solution*, and *Standard solution*

Suitability requirements

Resolution: NLT 2.0 between any adjacent peaks of benzothiadiazine related compound A, hydrochlorothiazide, amlodipine related compound A, amlodipine, valsartan related compound B, and valsartan, *System suitability solution*

Relative standard deviation: NMT 5.0% for amlodipine related compound A, benzothiadiazine related compound A, amlodipine, valsartan, and hydrochlorothiazide, *Standard solution*

Signal-to-noise ratio: NLT 10 for amlodipine, valsartan, and hydrochlorothiazide, *Sensitivity solution*

Analysis

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

Calculate the percentage of amlodipine related compound A 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 any 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 any 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 benzothiadiazine 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 benzothiadiazine related compound A from *Sample solution C*
r_S = peak response of benzothiadiazine related compound A from the *Standard solution*
C_S = concentration of USP Benzothiadiazine Related Compound A RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of hydrochlorothiazide in *Sample solution C* (mg/mL)

Calculate the percentage of chlorothiazide and hydrochlorothiazide dimer in the portion of Tablets taken:

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

r_U = peak response of chlorothiazide or hydrochlorothiazide dimer from *Sample solution C*
r_S = peak response of hydrochlorothiazide from the *Standard solution*
C_S = concentration of USP Hydrochlorothiazide RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of hydrochlorothiazide in *Sample solution C* (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 6*. Disregard the amlodipine ethyl analog peak, the valsartan related compound B peak, and any peaks below 0.1%.

Table 6

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A[a]	0.60	1.0
Chlorothiazide[b]	0.62	0.50
Hydrochlorothiazide	0.64	—
Devaleryl valsartan[c]	0.71	0.2
Hydrochlorothiazide dimer[d]	0.89	0.50
Amlodipine related compound A[e]	0.96	0.5
Amlodipine	1.00	—
Valsartan related degradation product 1[f]	1.04	0.2
Amlodipine ethyl analog[g]	1.08	—
Valsartan related compound B[h]	1.22	—

[a] 4-Amino-6-chloro-1,3-benzenedisulfonamide.
[b] 6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
[c] *N*-{[2′-(1*H*-Tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.
[d] 6-Chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine-4-yl 1,1-dioxide)methyl]3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
[e] 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
[f] These are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities.
[g] Diethyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. Process related impurity given for information only.
[h] ● *N*-Butyryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]-methyl}-L-valine. ● (IRA 1-Nov-2017) Process related impurity given for information only.
[i] Benzenesulfonic acid is the counter ion to the amlodipine, and peaks at RRT of 0.33 and 0.42 are not considered as degradation products.

Table 6 *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Valsartan related degradation product 2[f]	1.27	0.2
Valsartan	1.36	—
Valsartan related degradation product 3[f]	1.51	0.2
Valsartan related degradation product 4[f]	1.62	0.2
Any other unspecified degradation product[i]	—	0.2
Total degradation products	—	2.0

[a] 4-Amino-6-chloro-1,3-benzenedisulfonamide.
[b] 6-Chloro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
[c] *N*-{[2′-(1*H*-Tetrazole-5-yl)biphenyl-4-yl]methyl}-L-valine.
[d] 6-Chloro-*N*-[(6-chloro-7-sulfamoyl-2,3-dihydro-4*H*-1,2,4-benzothiadiazine-4-yl 1,1-dioxide)methyl]3,4-dihydro-2*H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.
[e] 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
[f] These are specified unidentified degradation products. No information is available about chemical structures or chemical names for these impurities.
[g] Diethyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate. Process related impurity given for information only.
[h] ● *N*-Butyryl-*N*-{[2′-(1*H*-tetrazole-5-yl)biphenyl-4-yl]-methyl}-L-valine.● (IRA 1-Nov-2017) Process related impurity given for information only.
[i] Benzenesulfonic acid is the counter ion to the amlodipine, and peaks at RRT of 0.33 and 0.42 are not considered as degradation products.

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 of valsartan related compound A and valsartan are about 0.65 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 the 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)

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 Benzothiadiazine Related Compound A RS
  4-Amino-6-chloro-1,3-benzenedisulfonamide.
  $C_6H_8ClN_3O_4S_2$ 285.73
  USP Hydrochlorothiazide RS
  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
  USP Valsartan Related Compound B RS
  ● (IRA 1-Nov-2017)

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Store at controlled room temperature in tight containers 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.