Amlodipine, Valsartan and Hydrochlorothiazide 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, Valsartan and Hydrochlorothiazide 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 92.5% and NMT 107.5%” for amlodipine, valsartan and hydrochlorothiazide.
- In the test for organic Impurities, the acceptance criteria for Benzothiadiazine related compound A is widened from NMT 0.4% to NMT 1.0%, Chlorothiazide and hydrochlorothiazide dimer from NMT 0.2% to NMT 0.50%, and the total degradation products is widened from NMT 1.5% to NMT 2.0%.
- 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, valsartan and hydrochlorothiazide are about 5.0 min and 7.5 min and 2.5 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 hydrochlorothiazide and valsartan are about 2.3 min and 3.6 min respectively. The typical retention time for amlodipine is about 2.8 min.

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

The Amlodipine, Valsartan and Hydrochlorothiazide Tablets Revision Bulletin supersede the currently official Amlodipine, Valsartan and Hydrochlorothiazide 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, Valsartan, and Hydrochlorothiazide Tablets

DEFINITION

Change to read:

Amlodipine, Valsartan, and Hydrochlorothiazide Tablets contain •NLT 92.5% and NMT 107.5%• (RB 1-Jun-2016) 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

Change to read:

- **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
Assay: 225 nm
Identification test A: Diode array, •UV 200–400 nm• (RB 1-Jun-2016)
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%• (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 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: 50 rpm 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); 55 rpm for 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide)

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: 5 µL for 10/320/25 (mg/mg/mg) of Tablet strengths (amlodipine/valsartan/hydrochlorothiazide); 10 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)

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 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*, 900 mL

L_2 = label claim for 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 for 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 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
Time: 30 min for valsartan and hydrochlorothiazide, 45 min for amlodipine
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 *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 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 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*, 900 mL
L_2 = label claim for 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 for 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: 50 rpm for valsartan and hydrochlorothiazide; 55 rpm for amlodipine in Tablets labeled to contain amlodipine/valsartan/hydrochlorothiazide, 10/320/25 (mg/mg/mg); and 50 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)
Times: 30 min for valsartan and hydrochlorothiazide, 45 min for amlodipine
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

Table 5 *(Continued)*

Time (min)	Solution A (%)	Solution B (%)
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 mL of the filtrate.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 237 for amlodipine and UV 270 nm for valsartan and hydrochlorothiazide
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 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)

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 for 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.● (RB 1-Jun-2016)

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

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*

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● (RB 1-Jun-2016) 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● (RB 1-Jun-2016) 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*.● (RB 1-Jun-2016) Disregard amlodipine ethyl analog peak, valsartan related compound B peak, and any peaks below 0.1%.

●**Table 6**● (RB 1-Jun-2016)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benzothiadiazine related compound A[a]	0.60	●1.0● (RB 1-Jun-2016)
●Chlorothiazide● (RB 1-Jun-2016)[b]	0.62	●0.50● (RB 1-Jun-2016)
Hydrochlorothiazide	0.64	—
Devaleryl valsartan[c]	0.71	0.2
●Hydrochlorothiazide dimer● (RB 1-Jun-2016)[d]	0.89	●0.50● (RB 1-Jun-2016)
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	—
Valsartan related degradation product 2[f]	1.27	0.2
Valsartan	1.36	—
Valsartan related degradation product 3[f]	1.51	0.2

[a] 4-Amino-6-chloro-1,3-benzenedisulfonamide.
●[b] 6-Chloro-2 *H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.● (RB 1-Jun-2016)
[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.● (RB 1-Jun-2016)
[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.● (RB 1-Jun-2016)
[h] (*S*)-*N*-Butyryl-*N*-{[2′-(1-*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine. ●Process related impurity given for information only.● (RB 1-Jun-2016)
[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**● (RB 1-Jun-2016) *(Continued)*

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Valsartan related degradation product 4[f]	1.62	0.2
Any other unspecified degradation product[i]	—	0.2
Total degradation products	—	●2.0● (RB 1-Jun-2016)

[a] 4-Amino-6-chloro-1,3-benzenedisulfonamide.

●[b] 6-Chloro-2 *H*-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide.● (RB 1-Jun-2016)

[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.● (RB 1-Jun-2016)

[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.● (RB 1-Jun-2016)

[h] (*S*)-*N*-Butyryl-*N*-{[2′-(1-*H*-tetrazole-5-yl)-biphenyl-4-yl]-methyl}-valine. ●Process related impurity given for information only.● (RB 1-Jun-2016)

[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.

ADDITIONAL REQUIREMENTS

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