Amlodipine and Atorvastatin Tablets

Type of Posting	Notice of Intent to Revise
Posting Date	26–Oct–2018
Targeted Official Date	To Be Determined, Revision Bulletin
Expert Committee	Chemical Medicines Monographs 2

In accordance with section 7.04 (c) of the 2015–2020 Rules and Procedures of the Council of Experts and the Pending Monograph Guideline, this is to provide notice that the Chemical Medicines Monographs 2 Expert Committee intends to revise the Amlodipine and Atorvastatin Tablets monograph.

Based on the supporting data received from a manufacturer awaiting FDA approval, the Expert Committee proposes to add *Dissolution Test 2* to the monograph.

- *Dissolution Test 2* was validated using an Agilent Zorbax Eclipse XDB-C18 brand of L1 column. The typical retention times for amlodipine and atorvastatin are about 0.46 and 3.9 min, respectively.

Labeling information has been incorporated to support the inclusion of *Dissolution Test 2*. The revision also necessitates a change in the table numbering in the tests for *Organic Impurities Related to Amlodipine* and *Organic Impurities Related to Atorvastatin*.

The proposed revision is contingent on FDA approval of a product that meets the proposed monograph specifications. The proposed revision will be published as a Revision Bulletin and an official date will be assigned to coincide as closely as possible with the FDA approval of the associated product.

See below for additional information about the proposed text.[1]

Should you have any questions, please contact Edith Chang, Ph.D., Senior Scientific Liaison (301-816-8392 or yec@usp.org).

[1] This text is not the official version of a *USP–NF* monograph and may not reflect the full and accurate contents of the currently official monograph. Please refer to the current edition of the *USP–NF* for official text.

USP provides this text to indicate changes that we anticipate will be made official once the product subject to this proposed revision under the Pending Monograph Program receives FDA approval. Once FDA approval is granted for the associated revision request, a Revision Bulletin will be posted that will include the changes indicated herein, as well as any changes indicated in the product's final approval, combined with the text of the monograph as effective on the date of approval. Any revisions made to a monograph under the Pending Monograph Program that are posted without prior publication for comment in the *Pharmacopeial Forum* must also meet the requirements outlined in the USP Guideline on Use of Accelerated Processes for Revisions to the *USP–NF*.

Add the following:

▲Amlodipine and Atorvastatin Tablets

DEFINITION

Amlodipine and Atorvastatin Tablets contain an amount of amlodipine besylate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and an amount of atorvastatin calcium equivalent to NLT 94.5% and NMT 105.0% of the labeled amount of atorvastatin ($C_{33}H_{34}FN_2O_5$). It may contain suitable antioxidants.

IDENTIFICATION

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

ASSAY

Change to read:

- **PROCEDURE**

Solution A: Dissolve 1.54 g of ammonium acetate in 1000 mL of water and add 2 mL of triethylamine. Adjust with acetic acid to a pH of 5.0.

Mobile phase: Acetonitrile, methanol, and *Solution A* (38:15:47)

Buffer: Transfer 7 mL of triethylamine to a 1000-mL volumetric flask containing 900 mL of water and mix. Adjust with dilute phosphoric acid (1 in 100) to a pH of 3.0 and dilute with water to volume.

Diluent: Acetonitrile, methanol, and *Buffer* (3:7:10)

Standard stock solution 1: 0.35 mg/mL of USP Amlodipine Besylate RS in methanol

Standard stock solution 2: 0.44 mg/mL of USP Atorvastatin Calcium RS in methanol

Standard solution: Prepare solutions of USP Amlodipine Besylate RS and USP Atorvastatin Calcium RS in *Mobile phase* at concentrations given in *Table 1* from *Standard stock solution 1* and *Standard stock solution 2*.

Table 1

Strength of Tablet, Amlodipine/Atorvastatin (mg/mg)	Concentration of Amlodipine Besylate (mg/mL)	Concentration of Atorvastatin Calcium (mg/mL)
2.5/10, 5/20, 10/40	0.028	0.088
2.5/20, 5/40, 10/80	0.014	0.088
5/10, 10/20	0.028	0.044
2.5/40, 5/80	0.014	0.176
10/10	0.028	0.022

Sample solution: Transfer NLT 10 Tablets to a suitable volumetric flask. Add about 20% of the final volume of the volumetric flask size in *Diluent* and sonicate to disperse the Tablets. Add about 40% of the final volume of the volumetric flask size in *Diluent*, sonicate for 20 min, and dilute with *Diluent* to volume. Centrifuge and transfer a suitable quantity of the supernatant to an appropriate suitable volumetric flask. Dilute with *Mobile phase* to volume to obtain the nominal concentrations of amlodipine and atorvastatin similar to that of the *Standard 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: 4.6-mm × 15-cm; 5-µm packing L1
Column temperature: 35°
Flow rate: 1 mL/min
Injection volume: 20 µL
Run time: NLT 3.5 times the retention time of amlodipine

System suitability
Sample: *Standard solution*
Suitability requirements
Tailing factor: NMT 2.0 for both peaks
Relative standard deviation: NMT 2.0% for both peaks

Analysis
Samples: *Standard solution* and *Sample solution*
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 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)
C_U = nominal concentration of amlodipine in the *Sample solution* (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 atorvastatin ($C_{33}H_{34}FN_2O_5$) in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times 100$$

r_U = peak response of atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, ▲1155.34▲ (ERR 1-Mar-2018)

Acceptance criteria
Amlodipine: 90.0%–110.0%
Atorvastatin: 94.5%–105.0%

PERFORMANCE TESTS

Change to read:

• **DISSOLUTION** ⟨711⟩

▲**Test 1**▲ (TBD)

Solution A, Mobile phase, Standard stock solution 1, Standard stock solution 2, Chromatographic system, and **System suitability:** Proceed as directed in the *Assay*.

Medium: 0.1% polysorbate 80 in pH 6.8 phosphate buffer; 900 mL

Apparatus 2: 75 rpm

Time: 20 min

Standard solution: (L_1/900) mg/mL of amlodipine and (L_2/900) mg/mL of atorvastatin in *Medium* from *Standard stock solution 1* and *Standard stock solution 2*, where L_1 is the label claim of amlodipine in mg/Tablet and L_2 is the label claim of atorvastatin in mg/Tablet

Sample solution: Centrifuge the solution under test and use the supernatant.

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

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

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 = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of atorvastatin ($C_{33}H_{34}FN_2O_5$) dissolved:

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

r_U = peak response of atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, ▲1155.34▲ (ERR 1-Mar-2018)
L = label claim of atorvastatin (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and atorvastatin ($C_{33}H_{34}FN_2O_5$) are dissolved.

▲**Test 2:** If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: 0.05 M phosphate buffer prepared as follows. Dissolve 40.8 g of potassium phosphate, monobasic and 5 g of sodium hydroxide in 6 L of water. Adjust with 1 N sodium hydroxide or phosphoric acid to a pH of 6.8; 900 mL.

Apparatus 2: 75 rpm

Time: 30 min

Buffer: Dissolve 4.0 g of sodium phosphate, monobasic in 1200 mL of water and add 6 mL of triethylamine. Adjust with phosphoric acid to a pH of 2.5.

Mobile phase: Acetonitrile and *Buffer* (40:60)

Diluent: Acetonitrile and water (50:50)

Standard stock solution 1: 155 µg/mL of USP Amlodipine Besylate RS in *Diluent*

Standard stock solution 2: 460 µg/mL of USP Atorvastatin Calcium RS in *Diluent*

Standard solution: Prepare solutions of USP Amlodipine Besylate RS and USP Atorvastatin Calcium RS at concentrations given in *Table 2* from *Standard stock solution 1* and *Standard stock solution 2*.

Table 2

Strength of Tablet, Amlodipine/ Atorvastatin (mg/mg)	Volume of Standard Stock Solution 1 to Be Added (mL)	Volume of Standard Stock Solution 2 to Be Added (mL)	Volume of Diluent to Be Added (mL)	Final Volume with Medium (mL)	Final Concentration of USP Amlodipine Besylate RS/ USP Atorvastatin Calcium RS (µg/mL)
5/10	10	5	45	200	7.75/11.5
5/20	10	10	40	200	7.75/23
5/40	10	20	30	200	7.75/46
5/80	10	40	10	200	7.75/92
10/10	20	5	35	200	15.5/11.5
10/20	20	10	30	200	15.5/23
10/40	20	20	20	200	15.5/46
10/80	20	40	–	200	15.5/92

Sample solution: Pass a portion of the solution under test through a suitable filter. Discard the first few milliliters of filtrate.

Chromatographic system

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

Mode: LC

Detector: UV 240 nm

Column: 4.6-mm × 5-cm; 1.8-µm packing L1

Column temperature: 50°

Flow rate: 2 mL/min

Injection volume: 20 µL

Run time: NLT 1.8 times the retention time of atorvastatin

System suitability

Sample: *Standard solution*

[NOTE—The relative retention times for amlodipine and atorvastatin are 0.12 and 1.0, respectively.]

Suitability requirements

Tailing factor: NMT 1.5 for amlodipine

Relative standard deviation: NMT 2.0% for amlodipine and atorvastatin

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) dissolved:

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

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 = label claim of amlodipine (mg/Tablet)

Calculate the percentage of the labeled amount of atorvastatin ($C_{33}H_{35}FN_2O_5$) dissolved:

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

r_U = peak response of atorvastatin from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
V = volume of *Medium*, 900 mL
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, 1155.34
L = label claim of atorvastatin (mg/Tablet)

Tolerances: NLT 80% (Q) of the labeled amount of amlodipine ($C_{20}H_{25}ClN_2O_5$) and atorvastatin ($C_{33}H_{35}FN_2O_5$) are dissolved.▲ (TBD)

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

IMPURITIES

Change to read:

- **ORGANIC IMPURITIES RELATED TO AMLODIPINE**

Buffer 1: Add 7 mL of triethylamine in 1000 mL of water and adjust with phosphoric acid to a pH of 2.5. Add 1.8 g of tetrabutylammonium hydrogen sulfate and mix well.
Solution A: Methanol and *Buffer 1* (40:60)
Solution B: Acetonitrile, methanol, and *Buffer 1* (40:40:20)
Mobile phase: See *Table* ▲3.▲ (TBD)

Table ▲3▲ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	90	10
2	90	10
7	75	25
16	70	30
18	55	45
24	25	75
30	10	90
31	0	100
35	0	100
36	90	10

Table ▲3▲ (TBD) *(continued)*

Time (min)	Solution A (%)	Solution B (%)
40	90	10

Buffer 2: Add 7 mL of triethylamine in 1000 mL of water. Adjust with phosphoric acid to a pH of 3.0.
Diluent 1: Methanol and water (50:50)
Diluent 2: Methanol and *Buffer 2* (50:50)
Standard stock solution: 0.7 mg/mL of USP Amlodipine Besylate RS in *Diluent 2*, prepared as follows. Transfer a suitable amount of USP Amlodipine Besylate RS to a suitable volumetric flask and dissolve in a quantity of methanol, about 20% of the volume of the flask. Dilute with *Diluent 2* to volume.
Standard solution 1: 5 µg/mL of USP Amlodipine Related Compound A RS in *Diluent 1*
Standard solution 2: 3.5 µg/mL of USP Amlodipine Besylate RS from *Standard stock solution* in *Diluent 2*
Sample solution: Nominally 0.5 mg/mL of amlodipine in *Diluent 2*, prepared as follows. Finely powder NLT 25 Tablets and transfer a portion of the powder, equivalent to 50 mg of amlodipine to a 100-mL volumetric flask. Add about 40 mL of methanol, shake to disperse, and sonicate for 15 min. Add about 40 mL of *Buffer 2* and sonicate for another 10 min. Dilute with *Diluent 2* to volume, centrifuge, and use the supernatant. Pass a portion of the solution through a suitable filter of 0.22-µm pore size. Prepare this solution fresh.
Chromatographic system
(See *Chromatography* ⟨621⟩*, System Suitability*.)
Mode: LC
Detector: UV 270 nm for amlodipine related compound A; 360 nm for all other impurities
Column: 2.1-mm × 15-cm; 1.8-µm packing L1
Column temperature: 40°
Flow rate: 0.3 mL/min
Injection volume: 5 µL
System suitability
Sample: *Standard solution 2*
Suitability requirements
Tailing factor: NMT 2.0
Relative standard deviation: NMT 5.0%
Analysis
Samples: *Standard solution 1*, *Standard solution 2*, and *Sample 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 the *Sample solution*
r_S = peak response of amlodipine related compound A from *Standard solution 1*
C_S = concentration of USP Amlodipine Related Compound A RS in *Standard solution 1* (mg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (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, 522.94

Calculate the percentage of atorvastatin–amlodipine adduct or any unspecified degradation product in the portion of Tablets taken:

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

r_U = peak response of each degradation product from the *Sample solution*
r_S = peak response of amlodipine from *Standard solution 2*
C_S = concentration of USP Amlodipine Besylate RS in *Standard solution 2* (mg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05
F = relative response factor (see *Table* ▲4▲ (TBD))

Acceptance criteria: See *Table* ▲4.▲ (TBD) Disregard peaks at the relative retention times of 2.18, 2.47 (atorvastatin), and 2.79 min.

Table ▲4▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Amlodipine related compound A	0.59	—	0.50
Amlodipine	1.00	—	—
Atorvastatin–amlodipine adduct[a]	3.49	0.47	0.50
Any unspecified degradation product	—	1.0	0.20
Total degradation products for amlodipine	—	—	1.0

[a] 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[(2-{(3*R*,5*R*)-7-[2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanamido}ethoxy)methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.

Change to read:

- **ORGANIC IMPURITIES RELATED TO ATORVASTATIN**

Buffer 1: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and adjust with dilute phosphoric acid (1 in 10) to a pH of 3.4.
Buffer 2: Dissolve 6.8 g of potassium dihydrogen phosphate in 1000 mL of water and adjust with triethylamine to a pH of 7.0.
Solution A: Tetrahydrofuran, acetonitrile, and *Buffer 1* (5:25:70)
Solution B: Tetrahydrofuran, acetonitrile, and *Buffer 2* (5:70:25)
Mobile phase: See *Table* ▲5.▲ (TBD)

Table ▲5▲ (TBD)

Time (min)	Solution A (%)	Solution B (%)
0	85	15
30	75	25
70	40	60
75	25	75
80	25	75
85	85	15
90	85	15

Diluent: Acetonitrile and water (50:50)
System suitability solution: Heat a suitable amount of USP Atorvastatin Calcium RS at 60° for 1 h for degradation; 0.55 mg/mL of degraded USP Atorvastatin Calcium RS, 3 µg/mL each of USP Atorvastatin Related Compound A RS, USP Atorvastatin Related Compound B RS, USP Atorvastatin Related Compound C RS, and USP Atorvastatin Related Compound H RS in *Diluent*. Sonication may be necessary for complete dissolution.
Standard solution: 2.7 µg/mL of USP Atorvastatin Calcium RS in *Diluent*
Sample solution: Nominally 0.5 mg/mL of atorvastatin in *Diluent*, prepared as follows. Transfer an amount equivalent to 50 mg of atorvastatin from a portion of NLT 20 finely powdered Tablets to a 100-mL volumetric flask. Add about 10 mL of acetonitrile, shake to disperse, and sonicate for 5 min. Add about 70 mL of *Diluent* and sonicate for another 20 min. Dilute with *Diluent* to volume and centrifuge. Prepare this solution fresh.
Chromatographic system
(See *Chromatography* ⟨621⟩, *System Suitability*.)
Mode: LC
Detector: UV 246 nm
Column: 4.6-mm × 25-cm; 4-µm packing L11
Column temperature: 45°
Flow rate: 1.2 mL/min
Injection volume: 20 µL
System suitability
Samples: *System suitability solution* and *Standard solution*
Suitability requirements
Resolution: NLT 1.0 between atorvastatin pyrrolidone analog and atorvastatin related compound A, *System suitability solution*
Relative standard deviation: NMT 5.0%, *Standard solution*
Analysis
Samples: *Standard solution* and *Sample solution*
Calculate the percentage of each atorvastatin specified or unspecified degradation product in the portion of Tablets taken:

$$\text{Result} = (r_U/r_S) \times (C_S/C_U) \times [M \times (M_{r1}/M_{r2})] \times (1/F) \times 100$$

r_U = peak response of each atorvastatin degradation product from the *Sample solution*
r_S = peak response of atorvastatin from the *Standard solution*
C_S = concentration of USP Atorvastatin Calcium RS in the *Standard solution* (mg/mL)
C_U = nominal concentration of atorvastatin in the *Sample solution* (mg/mL)
M = number of moles of atorvastatin per mole of atorvastatin calcium, 2
M_{r1} = molecular weight of atorvastatin, 558.64
M_{r2} = molecular weight of atorvastatin calcium, ▲1155.34▲ (ERR 1-Mar-2018)
F = relative response factor (see *Table* ▲6▲ (TBD))

Acceptance criteria: See *Table* ▲6.▲ (TBD) Disregard any impurity peaks less than 0.05% and the peaks from amlodipine related impurities.

Table ▲6▲ (TBD)

Name	Relative Retention Time	Relative Response Factor	Acceptance Criteria, NMT (%)
Atorvastatin pyrrolidone analog[a]	0.86	0.67	0.45
Atorvastatin related compound A[b]	0.91	—	—
Atorvastatin related compound B[b]	0.95	—	—
Atorvastatin	1.00	—	—
Atorvastatin related compound C[b]	1.04	—	—
Atorvastatin epoxy pyrrolooxazin 6-hydroxy analog[c]	1.35	0.39	0.5
Atorvastatin epoxy pyrrolooxazin 7-hydroxy analog[d]	1.40	0.52	0.5
Atorvastatin related compound H	1.78	1.0	1.0
Atorvastatin epoxy tetrahydrofuran analog[e]	1.96	0.63	0.5[g]
Atorvastatin oxirane[f]	2.23	1.0	
Atorvastatin *tert*-butyl ester[b, h]	2.55	—	—
Any unspecified degradation product	—	—	0.20
Total degradation products for atorvastatin	—	—	2.0
Total degradation products[i]	—	—	3.0

[a] (3*R*,5*R*)-7-[5-(4-Fluorophenyl)-3-isopropyl-2-oxo-4-phenyl-3-(phenylcarbamoyl)-2,3-dihydro-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid.
[b] Process impurity included in the table for identification only. Process impurities are controlled in the drug substance, and are not to be reported or included in the total impurities for the drug product.
[c] 4-{6-(4-Fluorophenyl)-7,8-epoxy-6-hydroxy-8a-isopropyl-7-phenyl-8-(phenylcarbamoyl)hexahydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-2-yl}-3-hydroxybutanoic acid.
[d] (3*R*)-4-(1b-(4-Fluorophenyl)-7-hydroxy-7-isopropyl-1a-phenyl-7a-(phenylcarbamoyl)hexahydro-1a*H*-oxireno[2′,3′:3,4]pyrrolo[2,1-*b*][1,3]oxazin-3-yl)-3-hydroxybutanoic acid.
[e] 4-(4-Fluorophenyl)-2,4-dihydroxy-2-isopropyl-*N*,5-diphenyl-3,6-dioxabicyclo[3.1.0]hexane-1-carboxamide.
[f] 3-(4-Fluorobenzoyl)-2-isobutyryl-*N*,3-diphenyloxirane-2-carboxamide.
[g] Sum of atorvastatin epoxy tetrahydrofuran analog and atorvastatin oxirane.
[h] (3*R*,5*R*)-*tert*-Butyl 7-(2-(4-fluorophenyl)-5-isopropyl-3-phenyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl)-3,5-dihydroxyheptanoate.
[i] Sum of the total degradation products for amlodipine from the test for *Organic Impurities Related to Amlodipine* and the total degradation products for atorvastatin from the test for *Organic Impurities Related to Atorvastatin*.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers. Store at controlled room temperature.

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.▲ (TBD)
- **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.
  $C_{20}H_{23}ClN_2O_5 \cdot C_4H_4O_4$ 522.94
  USP Atorvastatin Calcium RS
  USP Atorvastatin Related Compound A RS
  Calcium (3*R*,5*R*)-7-[2-isopropyl-4,5-diphenyl-3-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2).
  $C_{66}H_{70}CaN_4O_{10}$ 1119.38
  USP Atorvastatin Related Compound B RS
  (3*S*,5*R*)-7-[3-(Phenylcarbamoyl)-5-(4-fluorophenyl)-2-isopropyl-4-phenyl-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoic acid calcium salt.
  $C_{66}H_{68}CaF_2N_4O_{10}$ 1155.34
  USP Atorvastatin Related Compound C RS
  Calcium (3*R*,5*R*)-7-[2,3-Bis(4-fluorophenyl)-5-isopropyl-4-(phenylcarbamoyl)-1*H*-pyrrol-1-yl]-3,5-dihydroxyheptanoate (1:2).
  $C_{66}H_{66}CaF_4N_4O_{10}$ 1191.34
  USP Atorvastatin Related Compound H RS
  5-(4-Fluorophenyl)-1-{2-[(2*R*,4*R*)-4-hydroxy-6-oxotetrahydro-2*H*-pyran-2-yl]ethyl}-2-isopropyl-*N*,4-diphenyl-1*H*-pyrrole-3-carboxamide.
  $C_{33}H_{33}FN_2O_4$ 540.62▲ 1S (USP41)