

BRIEFING

Amlodipine and Benazepril Hydrochloride Capsules.

This monograph was posted on the USP Website as a draft USP Pending Monograph on Feb. 25, 2011, and has been available for review and public comment for more than 90 days. The SM2 Expert Committee reviewed the comment received and approved the monograph as an Authorized USP Pending Monograph.

Comment: The commenter indicated that the FDA-approved product has wider specifications for the specified, unspecified, and total impurities than those published in the pending monograph.

Response: Comment not incorporated. The SM2 Expert Committee determined that no action is required at this time. A monograph will be proposed for public comment in an upcoming issue of *PF*.

The liquid chromatographic procedures in the *Assay* and the tests for *Dissolution* and *Impurities* were validated using an Inertsil ODS 3V column containing 5- μ m packing L1. The typical retention times for amlodipine and benazepril are about 3.5 and 7 min, respectively, under the conditions in the *Assay*, and are about 12.5 and 14 min, respectively, under the conditions in *Impurities*.

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Amlodipine and Benazepril Hydrochloride Capsules

v.1 Authorized September 1, 2011

DEFINITION

Amlodipine and Benazepril Hydrochloride Capsules contain Amlodipine Besylate equivalent to NLT 90.0% and NMT 110.0% of the labeled amount of amlodipine free base and NLT 90.0% and NMT 110.0% of the labeled amount of benazepril hydrochloride.

IDENTIFICATION

- A.** The retention time of the major peak of the *Sample solution* corresponds to that of the *Standard solution*, as obtained in the *Assay*.

ASSAY

PROCEDURE

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Add 1 mL/L of triethylamine, and adjust with phosphoric acid to a pH of 3.0 ± 0.05 .

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

Amlodipine standard stock solution: 0.4 mg/mL of amlodipine from a suitable quantity of USP Amlodipine Besylate RS in *Mobile phase*. Sonicate for 5 min for complete dissolution.

Benazepril hydrochloride standard stock solution: 0.8 mg/mL of USP Benazepril Hydrochloride RS in *Mobile phase*. Sonicate for 5 min for complete dissolution.

Standard solutions: Using the *Amlodipine standard stock solution* and the *Benazepril hydrochloride standard stock solution*, prepare the solutions in *Mobile phase*, as directed in *Table 1*.

Table 1

Strength of Capsule [Amlodipine (mg)/Benazepril Hydrochloride (mg)]	Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
2.5/10	0.01/0.04
5/20	0.01/0.04
5/10	0.01/0.02

Table 1 (Continued)

Strength of Capsule [Amlodipine (mg)/Benazepril Hydrochloride (mg)]	Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
10/20	0.01/0.02
5/40	0.01/0.08
10/40	0.01/0.04

Sample stock solution: Transfer 10 intact Capsules into a 1-L flask. Add 600 mL of *Mobile phase*, and sonicate for about 20 min with occasional shaking. Dilute with *Mobile phase* to volume.

Sample solution: Dilute the *Sample stock solution* with *Mobile phase*, as directed in *Table 2*.

Table 2

Strength of Capsule [Amlodipine (mg)/Benazepril Hydrochloride (mg)]	Volume of Sample stock solution (mL)/ Final Volume (mL)
2.5/10	10/25
5/20	10/50
5/10	10/50
10/20	5/50
5/40	10/50
10/40	5/50

Pass through a membrane filter of 0.45- μ m pore size.

Chromatographic system

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

Mode: LC

Detector: UV 238 nm

Column: 4.6-mm \times 25-cm; 5- μ m packing L1

Column temperature: 35 $^{\circ}$

Flow rate: 1.5 mL/min

Injection size: 20 μ L

Run time: NLT 1.5 times the retention time of benazepril

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for both peaks

Relative standard deviation: NMT 1.5% for both peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of the labeled amount of amlodipine (C₂₀H₂₅ClN₂O₅) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of amlodipine in the *Standard solution* (mg/mL)

C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)

Calculate the percentage of the labeled amount of benazepril hydrochloride (C₂₄H₂₈N₂O₅ · HCl) in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*

r_S = peak response from the *Standard solution*

C_S = concentration of benazepril hydrochloride in the *Standard solution* (mg/mL)

C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 90.0%–110.0% of the labeled amount of amlodipine free base and 90.0%–110.0% of the labeled amount of benazepril hydrochloride

2 / Amlodipine

PERFORMANCE TESTS

• DISSOLUTION (711)

Medium: 0.01 N hydrochloric acid; 500 mL

Apparatus 1: 100 rpm

Time: 30 min

Buffer: 6.8 g/L of monobasic potassium phosphate in water. Add 1 mL/L of triethylamine. Adjust with phosphoric acid to a pH of 3.0 ± 0.05.

Mobile phase: Acetonitrile and Buffer (40:60)

Amlodipine standard stock solution: 0.5 mg/mL of amlodipine from USP Amlodipine Besylate RS in *Mobile phase*. Dilute this solution with *Medium* to obtain a final concentration of 0.05 mg/mL of amlodipine.

Benazepril hydrochloride standard stock solution: 2 mg/mL of USP Benazepril Hydrochloride RS in *Mobile phase*. Dilute this solution with *Medium* to obtain a final concentration of 0.2 mg/mL.

Standard solution: Dilute appropriate aliquots of the *Amlodipine standard stock solution* and *Benazepril hydrochloride standard stock solution* with *Medium* to obtain a final concentration of *L/500* for both drugs, where *L* is the Capsule label claim in mg.

Sample solution: Pass a portion of the solution under test through a suitable filter of 0.45-µm pore size.

Chromatographic system and System suitability:

Proceed as directed in the *Assay*.

Analysis

Samples: *Standard solution* and *Sample solution*
Calculate the percentage of the labeled amount of amlodipine (C₂₀H₂₅ClN₂O₅) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of amlodipine in the *Standard solution*
L = label claim for amlodipine (mg/Capsule)
M_{r1} = molecular weight of amlodipine, 408.88
M_{r2} = molecular weight of amlodipine besylate, 567.05

V = volume of *Medium*, 500 mL
Calculate the percentage of the labeled amount of benazepril hydrochloride (C₂₄H₂₈N₂O₅ · HCl) dissolved:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of benazepril in the *Standard solution*
L = label claim for benazepril (mg/Capsule)
V = volume of *Medium*, 500 mL

Tolerances: NLT 80% (Q) of the labeled amounts of amlodipine (C₂₀H₂₅ClN₂O₅) and benazepril hydrochloride (C₂₄H₂₈N₂O₅ · HCl) are dissolved.

• UNIFORMITY OF DOSAGE UNITS (905):

Meet the requirements

IMPURITIES

• PROCEDURE

Buffer: Proceed as directed in the *Assay*.

Solution A: Methanol and acetonitrile (70:30)

Solution B: 10 mL of tetrahydrofuran per L of *Solution A*

Mobile phase: See *Table 3*.

Table 3

Time (min)	Buffer (%)	Solution B (%)
0	60	40
15	48	52
35	40	60
45	30	70
50	30	70
52	60	40
60	60	40

Diluent: *Solution A* and *Buffer* (30:70)

Standard solution: 5 µg/mL each of amlodipine and amlodipine related compound A, and 10 µg/mL each of benazepril hydrochloride, benazepril related compound B, and benazepril related compound C in *Diluent*

Sample solution: Empty the contents of 10 Capsules into a suitable flask as directed in *Table 4*. Add *Diluent*, about 50% of the volume of the flask, and sonicate for 20 min. Dilute with *Diluent* to volume.

Table 4

Strength of Capsule [Amlodipine (mg)/Benazepril Hydrochloride (mg)]	Final Volume (mL)	Concentration of Amlodipine/Benazepril Hydrochloride (mg/mL)
2.5/10	50	0.5/2.0
5/20	100	0.5/2.0
5/10	100	0.5/1.0
10/20	200	0.5/1.0
5/40	100	0.5/4.0
10/40	200	0.5/2.0

Chromatographic system

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

Mode: LC

Detector: UV 238 nm

Column: 4.6-mm × 15-cm; 5-µm packing L1

Column temperature: 40°

Flow rate: 1.5 mL/min

Injection size: 20 µL

Run time: 4.2 times the retention time of benazepril

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 1.5 for the amlodipine and benazepril peaks

Relative standard deviation: NMT 2.0% for the amlodipine and benazepril peaks

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of amlodipine related compound A in the portion of Capsules taken:

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

r_U = peak response from the *Sample solution*
r_S = peak response from the *Standard solution*
C_S = concentration of amlodipine related compound A in the *Standard solution* (mg/mL)
C_U = nominal concentration of amlodipine in the *Sample solution* (mg/mL)
M_{r1} = molecular weight of amlodipine related compound A, 406.86
M_{r2} = molecular weight of amlodipine related compound A fumarate, 522.93

Calculate the percentage of benazepril related compound B and benazepril related compound C in the portion of Capsules taken:

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

r_U = peak response of benazepril related compound B or benazepril related compound C from the *Sample solution*
r_S = peak response of benazepril related compound B or benazepril related compound C from the *Standard solution*
C_S = concentration of benazepril related compound B or benazepril related compound C in the *Standard solution* (mg/mL)
C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of each individual unspecified impurity in the portion of Capsules taken:

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

- r_U = peak response of each individual unspecified impurity from the *Sample solution*
- r_S = peak response of benazepril from the *Standard solution*
- C_S = concentration of benazepril hydrochloride in the *Standard solution* (mg/mL)
- C_U = nominal concentration of benazepril hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: See Table 5.

Table 5

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benazepril related compound E ^a	0.11	—*
Benazepril related compound C ^b	0.27	3.0
Benazepril related compound F ^c	0.41	—*
Amlodipine related compound A ^d	0.59	0.5
Amlodipine	1.00	—*
Benazepril	1.20	—*
Amlodipine isopropyl analog ^{e,f}	1.33	—*
Amlodipine ethyl analog ^{g,f}	1.33	—*
Benazepril related compound B ^h	1.91	0.5
7-Bromo benazepril ^{i,j}	2.19	—*
Benazepril related compound D ^{k,i}	2.19	—*
Phthalyl amlodipine ^l	2.42	—*
Benazepril related compound G ^m	2.87	—*

- ^a 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.
- ^b {3-[1-Carboxy-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid.
- ^c 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid, *tert*-butyl ester.
- ^d 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
- ^e 3-Isopropyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^f Amlodipine isopropyl analog and amlodipine ethyl analog coelute at a relative retention time of 1.33.
- ^g Diethyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^h {3-[1-Ethoxycarbonyl-3-phenyl-(1*RS*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*SR*)-benzazepine}-1-acetic acid.
- ⁱ (3*S*)-7-Bromo-3-[[1*S*]-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, 3-ethyl ester, monohydrochloride.
- ^j 7-Bromo benazepril and benazepril related compound D coelute at a relative retention time of 2.19.
- ^k {3-[1-Ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid.
- ^l 3-Ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-[(2-[(2-methylcarbamoyl)benzamido]ethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate.
- ^m {3-[1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid ethyl ester.
- ⁿ {3-[1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid *t*-butyl ester.
- ^o 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[(2-(1,3-dioxoisindolin-2-yl)ethoxy)methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^p Total impurities include the sum of all specified impurities from amlodipine besylate and benazepril hydrochloride, excluding benazepril related compound C and the sum of all unspecified impurities. The process-related impurities are not included.
- ^q Disregard the peak due to benzene sulfonic acid at a relative retention time of 0.12.
- * This is a process related impurity and is controlled in the drug substance.

Table 5 (Continued)

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Benazepril <i>t</i> -butyl ester ^m	3.95	—*
Amlodipine phthalimide ^o	4.12	—*
Any other individual unspecified impurity	—	0.2
Total impurities ^{p,q}	—	1.5

- ^a 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.
- ^b {3-[1-Carboxy-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid.
- ^c 3-Amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid, *tert*-butyl ester.
- ^d 3-Ethyl 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate].
- ^e 3-Isopropyl 5-methyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^f Amlodipine isopropyl analog and amlodipine ethyl analog coelute at a relative retention time of 1.33.
- ^g Diethyl 2-[(2-aminoethoxy)methyl]-4-(2-chlorophenyl)-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^h {3-[1-Ethoxycarbonyl-3-phenyl-(1*RS*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*SR*)-benzazepine}-1-acetic acid.
- ⁱ (3*S*)-7-Bromo-3-[[1*S*]-1-carboxy-3-phenylpropyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, 3-ethyl ester, monohydrochloride.
- ^j 7-Bromo benazepril and benazepril related compound D coelute at a relative retention time of 2.19.
- ^k {3-[1-Ethoxycarbonyl-3-cyclohexyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid.
- ^l 3-Ethyl 5-methyl 4-(2-chlorophenyl)-6-methyl-2-[(2-[(2-methylcarbamoyl)benzamido]ethoxy)methyl]-1,4-dihydropyridine-3,5-dicarboxylate.
- ^m {3-[1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid ethyl ester.
- ⁿ {3-[1-Ethoxycarbonyl-3-phenyl-(1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine}-1-acetic acid *t*-butyl ester.
- ^o 3-Ethyl 5-methyl 4-(2-chlorophenyl)-2-[(2-(1,3-dioxoisindolin-2-yl)ethoxy)methyl]-6-methyl-1,4-dihydropyridine-3,5-dicarboxylate.
- ^p Total impurities include the sum of all specified impurities from amlodipine besylate and benazepril hydrochloride, excluding benazepril related compound C and the sum of all unspecified impurities. The process-related impurities are not included.
- ^q Disregard the peak due to benzene sulfonic acid at a relative retention time of 0.12.
- * This is a process related impurity and is controlled in the drug substance.

ADDITIONAL REQUIREMENTS

- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at controlled room temperature.
- **USP REFERENCE STANDARDS <11>**
 - USP Amlodipine Besylate RS
 - USP Benazepril Hydrochloride RS
 - USP Amlodipine Related Compound A RS
 - 3-Ethyl, 5-methyl [2-(2-aminoethoxymethyl)-4-(2-chlorophenyl)-6-methyl-3,5-pyridinedicarboxylate] fumarate.
 - C₂₀H₂₃ClN₂O₅ 522.93
 - USP Benazepril Related Compound B RS
 - (3*S*)-3-[[1*R*]-1-(Ethoxycarbonyl)-3-phenylpropyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-acetic acid, monohydrochloride.
 - C₂₄H₂₈N₂O₅ · HCl 460.95
 - USP Benazepril Related Compound C RS
 - 3-(1-Carboxy-3-phenyl-1*S*)-propyl]amino-2,3,4,5-tetrahydro-2-oxo-1*H*-1-(3*S*)-benzazepine-1-acetic acid.
 - C₂₂H₂₄N₂O₅ 396.44