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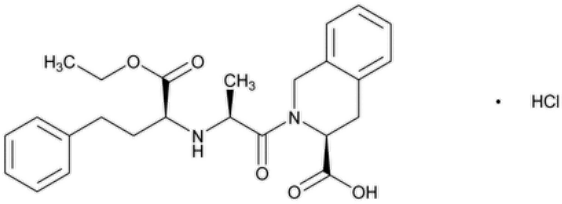
Quinapril Hydrochloride

Change to read:



$C_{25}H_{30}N_2O_5 \cdot HCl$ 474.98

3-Isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, [3*S*-[2[*R**(*R**)],3*R**]];

(*S*)-2-[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]-1,2,3,4-tetra hydro-3-isoquinolinecarboxylic acid, 1-ethyl ester, monohydrochloride;

▲(*S*)-2-{[(*S*)-1-Ethoxy-1-oxo-4-phenylbutan-2-yl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid hydrochloride.▲ (USP 1-May-2021) CAS RN®: 82586-55-8; UNII: 33067B3N2M.

▲Quinapril hydrochloride (acetone solvate):

$C_{25}H_{30}N_2O_5 \cdot HCl \cdot C_3H_6O$ 533.06 CAS RN®: 757964-89-9.▲ (USP 1-May-2021)

DEFINITION

Change to read:

Quinapril Hydrochloride contains NLT 98.5% and NMT 101.5% of quinapril hydrochloride ($C_{25}H_{30}N_2O_5 \cdot HCl$), calculated on the anhydrous basis.

▲If labeled as acetone solvate, it contains NLT 98.5% and NMT 101.5% of quinapril hydrochloride ($C_{25}H_{30}N_2O_5 \cdot HCl$) calculated on the anhydrous and acetone-free basis.▲ (USP 1-May-2021)

IDENTIFICATION

Change to read:

• **A.** **Spectroscopic Identification Tests ⟨197⟩, *Infrared Spectroscopy*:** 197K ▲or 197A▲ (USP 1-May-2021)

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

ASSAY

Change to read:

• **Procedure**

Mobile phase: Acetonitrile, methanesulfonic acid, and water (28: 0.1: 72)

Diluent: Acetonitrile and pH 6.5 0.025 M monobasic ammonium phosphate solution (40:60)

System suitability solution: 2 mg/mL of USP Quinapril Hydrochloride RS and 0.005 mg/mL each of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS in *Diluent*

Standard solution: 2 mg/mL of USP Quinapril Hydrochloride RS in *Diluent*

Sample solution: 2 mg/mL of Quinapril Hydrochloride in *Diluent*

Chromatographic system

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

Mode: LC

Detector: UV 214 nm

Columns

Guard: 4.6-mm × 3-cm; 5-µm packing L10

Analytical: 4.6-mm × 25-cm; 5-µm packing L10

Flow rate: 1.5 mL/min

Injection volume: 10 µL

▲Run time: NLT 3 times retention time of quinapril▲ (USP 1-May-2021)

System suitability

Samples: *System suitability solution*▲and *Standard solution*▲ (USP 1-May-2021)

Suitability requirements

Resolution: NLT 1.75 between quinapril and quinapril related compound A; NLT 3.5 between quinapril and quinapril related compound B, ▲*System suitability solution*

Tailing factor: NMT 2.0, *Standard solution*▲ (USP 1-May-2021)

Relative standard deviation: NMT ▲0.55%, *Standard solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of quinapril hydrochloride ($C_{25}H_{30}N_2O_5 \cdot HCl$) in the portion of Quinapril Hydrochloride taken:

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

r_U = peak response of quinapril ▲▲ (USP 1-May-2021) from the *Sample solution*

r_S = peak response of quinapril ▲▲ (USP 1-May-2021) from the *Standard solution*

C_S = concentration of USP Quinapril Hydrochloride RS in the *Standard solution* (mg/mL)

C_U = concentration of Quinapril Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 98.5%–101.5% on the anhydrous basis ▲and 98.5%–101.5% on the anhydrous and acetone-free basis if labeled as acetone solvate▲ (USP 1-May-2021)

OTHER COMPONENTS

• **Content of Chloride**

Sample: 100 mg of Quinapril Hydrochloride

Titrimetric system

(See *Titrimetry ⟨541⟩*.)

Mode: Direct titration

Titrant: 0.01 N silver nitrate VS

Analysis: Transfer the *Sample* to a 100-mL beaker. Dissolve in 50 mL of water and 10 mL of alcohol, and acidify with nitric acid. Titrate with *Titrant* using suitable electrodes. Perform a blank determination, and make any necessary corrections. Each milliliter of 0.01 N silver nitrate is equivalent to 0.3545 mg of chloride.

Acceptance criteria: 7.2%–7.6%

IMPURITIES

• **Residue on Ignition ⟨281⟩:** NMT 0.1%

Delete the following:

▲• **Limit of Residual Solvents**

Standard stock solution: Transfer 50 mL of dimethylformamide to a 200-mL volumetric flask. Add 75 mg each of acetone and acetonitrile and 30 mg each of methylene chloride and toluene, each weighed by difference. Dilute with dimethylformamide to volume.

Standard solution: 4.0 mL of the *Standard stock solution*, diluted with dimethylformamide to 50 mL

System suitability solution 1: Transfer 25 mL of dimethylformamide to a 50-mL volumetric flask. Add 35 µL of dehydrated alcohol and 25 µL of methylene chloride. Dilute with dimethylformamide to volume. Transfer 1.0 mL of this solution to a 50-mL volumetric flask, and dilute with dimethylformamide to volume.

System suitability solution 2: 2.0 mL of the *Standard stock solution*, diluted with dimethylformamide to 50 mL

Sample solution: 60 mg of Quinapril Hydrochloride to a suitable headspace vial, add 5.0 mL of dimethylformamide, seal, and shake to dissolve.

Chromatographic system

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

Mode: GC

Detector: Flame ionization

Column: 0.53-mm × 30-m fused silica column coated with a 1.0-µm film of phase G16 and a split injection system

Carrier gas: Helium

Flow rate: 6 mL/min

Sampler: Headspace

Vial pressure: 6.1 psi

Split flow rate: 100 mL/min (back pressure of 3.5 psi)

Injection volume: 1 mL

Temperature

Injector port: 180°

Detector: 240°

Oven temperature of the headspace sampler: 60°

Headspace loop and transfer lines: 65°

[NOTE—The vials are equilibrated for 10 min prior to injection, and injection occurs every 36 min.]

Column temperature: See the temperature table below.

Initial Temperature (°)	Temperature Ramp (°/min)	Final Temperature (°)	Hold Time at Final Temperature (min)
35	0	35	10
35	7	150	4

System suitability

Samples: *System suitability solution 1* and *System suitability solution 2*

[NOTE—The relative retention times for methylene chloride and alcohol are about 0.94 and 1.0, respectively, *System suitability solution 1*.]

Suitability requirements

Resolution: NLT 1.2 between methylene chloride and alcohol, *System suitability solution 1*

Column efficiency: NLT 4900 theoretical plates, from the methylene chloride peak of *System suitability solution 1*

Tailing factor: NMT 1.7 for the methylene chloride peak, *System suitability solution 1*

Relative standard deviation: NMT 15.0%, *System suitability solution 2*

Analysis

Samples: *Standard solution* and *Sample solution*

Separately calculate the percentages, by weight, of acetone, acetonitrile, methylene chloride, and toluene in the portion of Quinapril Hydrochloride taken:

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

r_U = peak response of the relevant solvent of the *Sample solution*

r_S = peak response of the relevant solvent of the *Standard solution*

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

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

Acceptance criteria

Acetone: NMT 0.25%

Acetonitrile: NMT 0.25%

Methylene chloride: NMT 0.1%

Toluene: NMT 0.1%▲ (USP 1-May-2021)

Change to read:

• **ORGANIC IMPURITIES**

Mobile phase, Diluent, System suitability solution, Sample solution, and **Chromatographic system:** Proceed as directed in the *Assay*.

▲**Sensitivity solution:** 2 µg/mL of USP Quinapril Hydrochloride RS in *Diluent*▲ (USP 1-May-2021)

Standard solution: 5 µg/mL each of USP Quinapril Related Compound A RS and USP Quinapril Related Compound B RS in *Diluent*

▲**System suitability**

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

Suitability requirements

Resolution: NLT 1.75 between quinapril and quinapril related compound A; NLT 3.5 between quinapril and quinapril related compound B, *System suitability solution*

Relative standard deviation: NMT 2.0%, *Standard solution*

Signal-to-noise ratio: NLT 10, *Sensitivity solution*▲ (USP 1-May-2021)

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of quinapril related compound A or quinapril related compound B in the portion of Quinapril Hydrochloride taken:

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

r_U = peak response of quinapril related compound A or quinapril related compound B from the *Sample solution*

r_S = peak response of quinapril related compound A or quinapril related compound B from the *Standard solution*

C_S = concentration of USP Quinapril Related Compound A RS or USP Quinapril Related Compound B RS in the *Standard solution* (mg/mL)

C_U = concentration of Quinapril Hydrochloride in the *Sample solution* (mg/mL)

Calculate the percentage of any individual unspecified impurity in the portion of Quinapril Hydrochloride taken:

$$\text{Result} = (r_U/r_T) \times 100$$

r_U = peak response of any individual unspecified impurity from the *Sample solution*

r_T = sum of the responses of all the peaks from the *Sample solution*

Acceptance criteria: See *Table 1*.

Table 1

Name	Relative Retention Time	Acceptance Criteria, NMT (%)
Quinapril related compound B	0.54	0.5
Quinapril	1.00	—
Quinapril related compound A	1.85	0.5
Any individual unspecified impurity	—	0.2
Total impurities	—	2.0

SPECIFIC TESTS

Add the following:

▲• **Content of Acetone** (if labeled as acetone solvate)

Solution A: Water

Solution B: Acetonitrile

Mobile phase: See *Table 2*.

Table 2

Time (min)	Solution A (%)	Solution B (%)
0	98	2
2.0	98	2
2.1	40	60
5.0	40	60
5.1	98	2
7.0	98	2

Standard solution: 1.0 mg/mL of USP Acetone RS in water prepared as follows. Weigh and transfer an appropriate amount of USP Acetone RS to a suitable volumetric flask containing 50% of the final volume of water. Dilute with water to volume.

Sample solution: 10 mg/mL of Quinapril Hydrochloride in water. Sonicate if necessary.

Chromatographic system

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

Mode: LC

Detector: UV 264 nm

Column: 4.6-mm × 10-cm; 2.6-µm packing L1

Temperatures

Autosampler: 20°

Column: 35°

Flow rate: 2.0 mL/min

Injection volume: 50 µL

System suitability

Sample: *Standard solution*

Suitability requirements

Tailing factor: NMT 2.0

Relative standard deviation: NMT 1.0%

Analysis

Samples: *Standard solution* and *Sample solution*

Calculate the percentage of acetone in the portion of Quinapril Hydrochloride as acetone solvate taken:

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

r_U = peak response of acetone from the *Sample solution*

r_S = peak response of acetone from the *Standard solution*

C_S = concentration of USP Acetone RS in the *Standard solution* (mg/mL)

C_U = concentration of Quinapril Hydrochloride in the *Sample solution* (mg/mL)

Acceptance criteria: 7.9%–13.9%▲ (USP 1-May-2021)

- **Water Determination ⟨921⟩, *Method I*:** NMT 1.0%
- **Optical Rotation ⟨781S⟩, *Procedures, Specific Rotation***

Sample solution: 20 mg/mL in methanol

Acceptance criteria: +14.4° to +15.4°

ADDITIONAL REQUIREMENTS

Change to read:

- **Packaging and Storage:** Preserve in well-closed containers, and store at controlled room temperature. ▲If labeled as an acetone solvate, store in a tight container filled with nitrogen at controlled room temperature.▲ (USP 1-May-2021)

Add the following:

▲• **Labeling:** Where it is an acetone solvate form, the label so indicates.▲ (USP 1-May-2021)

Change to read:

• **USP Reference Standards** ⟨11⟩

▲ USP Acetone RS▲ (USP 1-May-2021)

USP Quinapril Hydrochloride RS

USP Quinapril Related Compound A RS

Ethyl [3*S*-[(2*R**), 3a, 11ab]]-1,3,4,6,11,11a-hexahydro-3-methyl-1,4-dioxo-a-(2-phenylethyl)-2*H*-pyrazino[1,2-b]isoquinoline-2-acetate;

▲Also known as Ethyl (*S*)-2-{(3*S*,11a*S*)-3-methyl-1,4-dioxo-1,3,4,6,11,11a-hexahydro-2*H*-pyrazino[1,2-*b*]isoquinolin-2-yl}-4-phenylbutanoate.

$C_{25}H_{28}N_2O_4$ 420.51▲ (USP 1-May-2021)

USP Quinapril Related Compound B RS

3-Isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, [3*S*-[2[*R**(*R**)],3*R**]];

▲Also known as (*S*)-2-{[(*S*)-1-Carboxy-3-phenylpropyl]-L-alanyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.▲ (USP 1-May-2021)

$C_{23}H_{26}N_2O_5$ 410.47

Auxiliary Information - Please check for your question in the FAQs before contacting USP.

Topic/Question	Contact	Expert Committee
QUINAPRIL HYDROCHLORIDE	Documentary Standards Support	SM22020 Small Molecules 2
REFERENCE STANDARD SUPPORT	RS Technical Services RSTECH@usp.org	SM22020 Small Molecules 2

Chromatographic Database Information: Chromatographic Database

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